FORMULATION DEVELOPMENT AND EVALUATION OF UBIDECARENONE CHEWABLE TABLETS

A dissertation submitted to

THE TAMILNADU DR. M.G.R. MEDICAL UNIVERSITY

CHENNAI – 600 032

in partial fullfillment of the requirements for the award of degree of

MASTER OF PHARMACY

IN

PHARMACEUTICS

Submitted by

Reg. No. 26108304

under the guidance of

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DATE:

This is to certify that the dissertation entitled ***"Formulation Development and Evaluation of Ubidecarenone Chewable Tablets"*** submitted by the candidate bearing **Register No. 26108304** for The Tamil Nadu Dr. M.G.R. Medical University examinations.

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CERTIFICATE

This is to certify that the dissertation entitled **"Formulation Development and Evaluation of Ubidecarenone Chewable Tablets"** submitted by the candidate bearing Reg. No. 26108304 in partial fulfillment of the requirements for the award of the degree of **MASTER OF PHARMACY** in **PHARMACEUTICS** by The Tamil Nadu Dr.M.G.R. Medical University is a bonafide work done by him during the academic year 2011-2012.

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DEDICATED TO

MY PARENTS

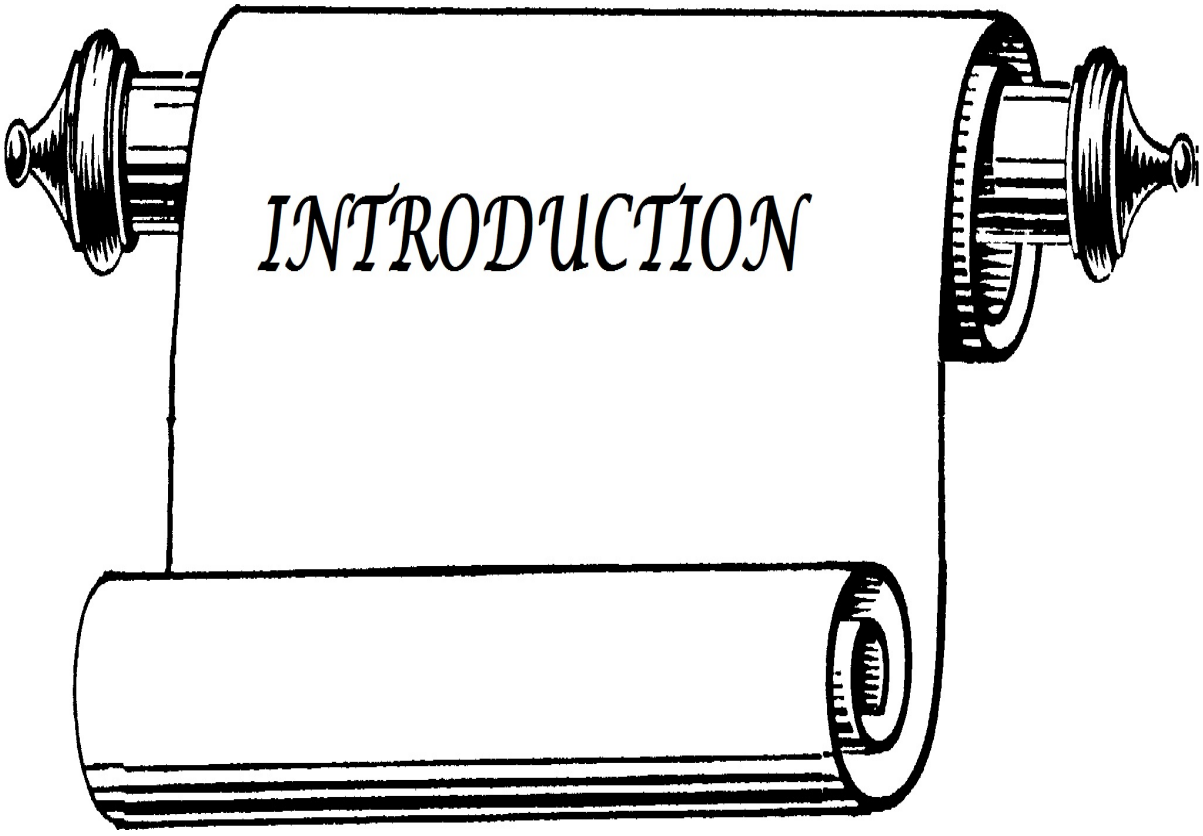
&

MY WELL WISHERS

LIST OF ABBREVIATIONS

UB	Ubidecarenone
NC	No Change
ASTM	American Standards for Testing Materials
KF	Karl Fischer
HDPE	High Density Poly Ethylene
Min	Minutes
Sec	Seconds
RH	Relative humidity
PP	Polypropylene
NMT	Not more than
NLT	Not less than
SLS	Sodium lauryl sulphate
cc	Cubic Centimeter
Kp	Kilopond
USP	United States Pharmacopoeia
BP	British Pharmacopoeia
JP	Japanese Pharmacopoeia
mL	Millilitre
SD	Standard deviation
mg	Milligram
RS	Reference Standard
CoQ10	Coenzyme Q10
HPLC	High performance liquid chromatography

CONTENTS

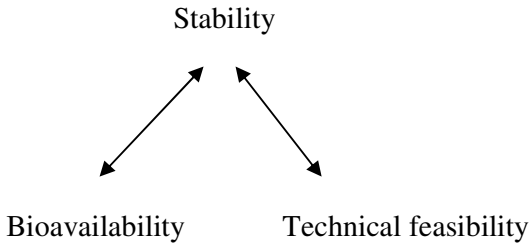

INTRODUCTION

1. INTRODUCTION

1.1 SOLID ORAL DOSAGE FORMS [1]

Oral solid dosage forms such as tablets and hard gelatin capsules, which have been in existence since 19th century, remain the most frequently used dosage forms. Oral route of delivery is a route that the patient understands and accepts. For the manufacturer solid oral dosage forms offer many advantages: they utilize cheap technology, are generally the most stable forms of drugs, are compact and their appearance can be modified to create brand identification.

Tablets and capsules are very versatile. When formulating any pharmaceutical dosage form, it is important to remember that there is equilibrium between the bioavailability of the product, its chemical and physical stability and the technical feasibility of producing it.



Any change made to a formulation in an attempt to optimize one of these properties is likely to have an effect on the other two parameters, which must be considered. This is especially true of immediate-release solid dosage forms. Many of the properties required to optimize the bioavailability through rapid disintegration and dissolution of the active constituent, for example small particle size must be balanced with the manufacturability, where the fluidity and compatibility of a powder will often be enhanced by an increase in particle size. Tablets and hard gelatin capsules form the vast majority of solid dosage forms on the market. While the actual processes involved of filling capsules and compressing tablets differ, the preparations of the powders to be processed are, in many cases, very similar.

1.2 TYPES OF SOLID DOSAGE FORMS [1]

There are many different types of tablets which can be designed to fulfill specific therapeutic needs.

Table 1: Types of Solid Dosage Forms

Formulation type	Description
Immediate release tablets	The dosage form is designed to release the drug substance immediately after ingestion.
Chewable tablets	Strong, hard tablets to give good mouth feel.
Lozenges	Strong, slowly dissolving tablets for local delivery to mouth or throat. Often prepared by a candy molding process.
Buccal tablets	Tablets designed to be placed in buccal cavity of mouth for rapid action.
Effervescent tablets	Taken in water, the tablet forms an effervescent, often pleasant-tasting drink.
Dispersible tablets	Tablets taken in water, the tablet forms a suspension for ease of swallowing.
Soluble tablets	Tablets taken in water, the tablet forms a solution for ease of swallowing.
Hard gelatin capsules	Two-piece capsule shells, which can be filled with powders, pellets, semisolids or liquids.
Soft gelatin capsules	One-piece capsules containing a liquid or semisolid fill.
Pastilles	Intended to dissolve in mouth slowly for the treatment of local infections. Usually composed of a base containing gelatin and glycerin.

1.3 Advantages of solid oral dosage forms [2]

- They are unit dosage forms and offer the greatest capabilities of all oral dosage forms for the greatest dose precision and least content variability.
- Low cost among all dosage forms.
- They are lightest and most compact dosage forms.
- They are easiest and cheapest to package and ship.
- Product identification requires no additional processing steps when employing an embossed or monogrammed punch face.
- Easy large scale production.
- They have the best combined properties of chemical, mechanical and microbiological stability among all dosage forms.
- Drugs with bitter taste, objectionable odour, sensitivity towards oxygen or hygroscopic nature may require encapsulation/entrapment prior to compression or coating of tablets is required. In such cases, the capsule could be prepared.

1.4 Disadvantages

- Some drugs having resistance for compression into dense compacts owing to their amorphous nature or flocculent and low density properties.
- Drugs with bitter taste, objectionable odour, sensitivity towards oxygen or hygroscopic nature may require encapsulation or coating of tablets.
- Elderly, ill and children could have the problem in swallowing the tablets.

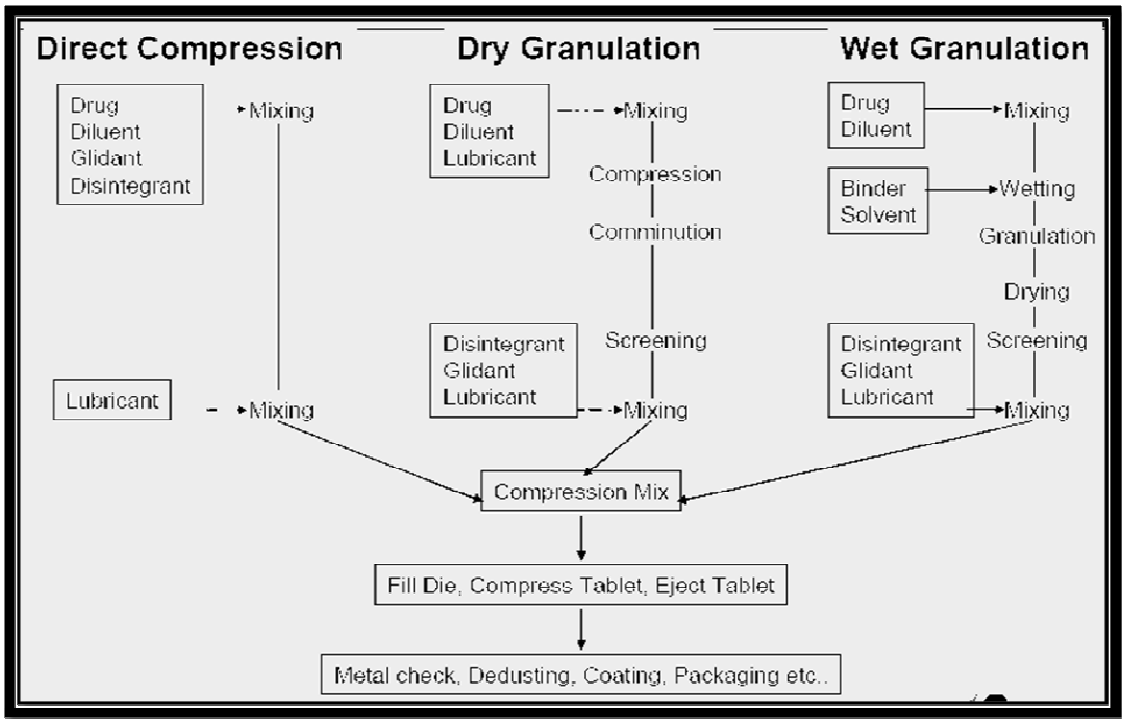


Fig 1: Various Granulation Techniques

1.5 PROCESS INVOLVED IN MANUFACTURING OF ORAL SOLID DOSAGE FORMS [3]

Tablet formulations have been prepared by one of two methods:

1. Direct compression
2. Granulation.

1.5.1 DIRECT COMPRESSION

Direct compression is the term used to define the process where powder blends of the drug substance and excipients are compressed on a tablet machine. There is no mechanical treatment of the powder apart from a mixing process. It was only used for inorganic materials such as potassium bromide. Today, within the pharmaceutical industry, the term is used for tablet manufacture that does not involve the pre-treatment of the drug substance apart from blending with excipients.

1.5.2 Advantages

- Simplicity and subsequent economy.
- The omission of a drying step results in lower energy consumption.
- No need of granulators, driers.
- Savings in labour cost as well as time.
- Stability of certain drugs can be improved by the elimination of a wetting and drying process when formulating drugs that are thermolabile or moisture sensitive.

1.5.3 Disadvantages

- It cannot be used for all drug substances.
- The technique depends on the major components of the formulation having appropriate flow and compaction properties.
- Low-dose drugs by direct compression are related to achieving and maintaining a homogeneous mix.

1.5.4. GRANULATION[4]

Granulation is the most widely used technique to prepare powders for compaction. A number of methods can be used to achieve the agglomeration.

Granulation is classified as

- **Wet granulation** - where a liquid is used to aid the agglomeration process.
- **Dry granulation** - where no liquid is used.

The purpose of granulating is to transform the powdered starting material into granules that will run smoothly on a tablet machine. The granulation process usually involves the addition of a polymeric binder that sticks the individual particles together. The polymers used as binders are usually hydrophilic in nature. This can have a beneficial effect on the dissolution of hydrophobic drugs. During the granulation process, a film of hydrophilic polymer will form over the surface of hydrophobic drug particles, which will aid wetting.

1.5.5 WET GRANULATION

Wet granulation is the most commonly used method in tablet manufacture. These methods involve the addition of a liquid usually a polymeric binder to the powdered starting materials, and a form of agitation to promote agglomeration followed by a drying

process. In most cases, the liquid used is water, although in certain circumstances organic solvents such as ethanol or ethanol/water mixtures are used. Non aqueous granulation will be considered when the active substance is particularly unstable in the presence of water, when water will not wet the powder or possibly if the drug substance forms a significant portion of the granulate and demonstrates extreme solubility in aqueous media and control of the granulation process becomes difficult due to the occurrence of significant dissolution.

There are a number of approaches to wet granulation used in the Pharmaceutical industry, they all share the following basic principles

- **Dry mixing**

The starting materials are mixed together. Prior to mixing, the ingredients may be deagglomerated by a milling or sieving process. If the granulate has a low drug content, the active substance may be premixed with one of the ingredients prior to being added to the granulation vessel to ensure good content uniformity.

- **Addition of granulating liquid**

The granulating fluid is added to the dry ingredients and mixed to form a wet mass. The mixing of the fluid with the dry ingredients leads to agglomeration of the powder. This agglomeration can be controlled by altering the amount of fluid added, the intensity of the mixing and the duration of the mixing. Depending on the state of agglomeration achieved, this stage may be followed by a wet sieving process to break up the larger agglomerates.

- **Drying**

The fluid is removed by drying process.

- **Milling**

The dried granulate undergoes a sieving or milling operation to obtain the desired particle size distribution.

1.5.6 DRY GRANULATION [5]

Dry granulation involves the aggregation of particles by high pressure to form bonds between particles by virtue of their close proximity. Two approaches to dry granulation are used in the pharmaceutical industry

- Slugging
- Roller compaction.

➢ Slugging

Granulation by slugging is the manufacture of large compacts by direct compression. The slugs produced are larger than tablets and are often poorly formed tablets exhibiting cracking and lamination. As with tablets, it may be necessary to add a lubricant to prevent the compacts sticking to the punches and dies. The compressed material is broken up and sieved to form granules of the appropriate size. The granules are then blended with disintegrant, lubricant and compressed on a normal tablet punching machine.

➢ Roller compaction

In roller compaction, the powder is compacted by means of pressure rollers. It is fed between two cylindrical rollers, rotating in opposite directions. By means of a hydraulic ram forcing one of the rollers against the other, machine is capable of exerting known fixed pressures on any powdered material that flows between the rollers. Powdered material is fed between the rollers by a screw conveyor system. After passing through the rollers, the compacted mass resembles a thin wide ribbon that has fallen apart into large segments. These are equivalent to the slugs produced by the slugging process. The segments are then screened or milled for the production of granules. Roller compaction is done by using chilsonator.

1.6 CHEWABLE TABLETS[6]

Chewable tablets are tablets that are required to be broken and chewed in-between the teeth before ingestion. These tablets are given to children who have difficulty in swallowing and to the adults who dislike swallowing. Chewable tablets are chewed and broken into smaller pieces prior to swallowing and are not to be swallowed intact. In this way, the time required for disintegration is reduced and the rate of absorption of the medicament may increase. For the preparation of chewable tablets, mannitol is used as the base. These tablets should have acceptable taste and flavour. They should disintegrate in a short time and produce cool sweet taste.

❖ **Advantages**

- Better bioavailability through bypassing disintegration and perhaps enhancing dissolution.
- Patient convenience through the elimination of the need of water for swallowing (chewable tablets can be taken at any places even if water is not available).
- Possible use as a substitute for liquid dosage forms where rapid onset of action is desired.
- Minimized first pass effect.
- Improved patient acceptance especially in paediatrics through pleasant taste and product distinctiveness.
- For both physiological and psychological reasons, children up to the young teens usually have trouble in swallowing tablets and capsules. In such cases, chewable tablets are preferable because of their patient acceptability (palatability) and better stability.
- Easily accessible for self-medication.
- Possible to achieve an effective taste masking along with a pleasant mouth feel.

❖ **Disadvantages**

- Extremely bad tasting drugs cannot be formulated as chewable tablets.
- Drugs that have extremely high dosage levels are difficult to formulate.
- Chewable tablets are to be sipped slowly for longer period of time (wrong usage such as swallowing like conventional tablets leads to reduced therapeutic efficacy).

❖ **Requirements**

- Less grittiness.
- Creamier mouth feel.
- Improved overall palatability (Good taste and mouth feel).
- Acceptable bioavailability and bioactivity.
- Acceptable stability and quality.
- Economical formula and process.

1.6.1 FORMULATION TECHNIQUES [7]

COATING BY WET GRANULATION

❖ **Microencapsulation**

Microencapsulation is a method of coating drug particles or liquid droplets with edible polymeric materials, thereby masking the taste and forming relatively free flowing microcapsules of 5 – 5000μm size. The most common method for taste masking application is phase separation or coacervation technique. The resultant coated granules not only mask the taste of a drug but also minimize the physical and chemical incompatibility between ingredients. However, this method is more expensive and requires specialized equipment and knowledgeable personnel. Coagulable water soluble egg albumin is used as coating medium for masking the taste of erythromycin.

➢ **Solid dispersions**

Bad tasting drugs can be prevented from stimulating the taste buds by adsorption onto substrates capable of keeping the drugs adsorbed while in the mouth but releasing them eventually in the stomach or gastrointestinal tract.

ADSORBATE FORMATION TECHNIQUES

➢ **Solvent method**

The formation of an adsorbate involves dissolving the drug in a solvent, mixing the solution with the substrate and evaporating the solvent that leaves the drug molecules adsorbed upon the substrate. The variables of the process such as choice of solvent, substrate, proportions, mixing conditions, rate of evaporation and temperature must be optimized to give the desired product.

- **Melting method**

The drugs and a carrier are melted together by heating. The molten mixture is then cooled and rapidly solidified in an ice bath with vigorous stirring. The product is then pulverized and sized. Heat labile drugs, volatile drugs and drug that decompose on melting are unsuitable for this method. The method is simple with low cost and no problem of residual solvents as in solvent evaporation method.

- **Ion Exchange**

In this technique, the ion exchange materials acts as a drug carrier that helps in binding of drugs into an insoluble polymeric matrix and can effectively mask the problems of taste and odour in drugs to be formulated as chewable tablets.

- **Spray congealing and spray coating**

The process of spray congealing involves cooling of melted substances in the form of fine particles during their travel from a spray nozzle into the spraying chamber held at a temperature below their melting point. If slurry of drug material insoluble in a melted mass is spray-congealed, discrete particles of the insoluble material coated with the congealed substance is obtained. The process of spray coating involves the spraying of a suspension of the drug particles in a solution of the coating material through an atomizer into a high-velocity stream of warm air. The coarse droplets delivered by the atomizer consist of drug particles enveloped by coating solution. As the solvent evaporates, the coating material encapsulates the drug particle.

- **Formation of different salts or derivatives**

In this, an attempt is made to modify the chemical composition of the drug substance itself, to render it less soluble in saliva and thereby less stimulating for the taste buds or to obtain a tasteless or less bitter form.

- **Use of amino acids and protein hydrolysates**

By combining amino acids, their salts or a mixture of two, it is possible to reduce the bitter taste. The preferred amino acids are sacrosine, alanine, taurine, glutamic acid and glycine.

- **Inclusion complexes**

In inclusion complex formation, the drug molecule (guest molecule) fits into the cavity of a complexing agent (host molecule) forming a stable complex. The complex is capable of masking the bitter taste of the drug. The most commonly used complexing agent is cyclodextrin.

- **Molecular complexes**

Molecular complex formation involves a drug and a complexing organic molecule. In this, masking of bitter taste or odour of drugs is achieved by forming complexes that would lower the aqueous solubility of the drug and thus the amount of drug in contact with the taste buds.

1.6.2 ORGANOLEPTIC CONSIDERATIONS [6]

- **Taste**

From the perspective of consumer acceptance, taste is almost certainly the most important parameter for the evaluation of chewable tablets. Taste is a combination of the perceptions of mouth-feel, sweetness and flavour. Taste is a sensory response resulting from a stimulation of the taste buds on the tongue. There are four basic types of taste: salty, sour, sweet and bitter. Salty or sour taste is derived from substances capable of ionizing in solution.

Many organic medications exhibit a bitter response even though they may not be capable of ionizing in an aqueous medium. Substances incapable of producing a sensory stimulation of the taste buds are referred to as bland or tasteless. Sweetness at an appropriate level is a necessary background to a flavour. The primary contributors to sweetness in a chewable tablet are the drug, natural sweeteners and artificial sweetness enhancers that may be incorporated in the formulation.

- **Aroma**

Pleasant smells are generally referred to as aromas.

For example: Orange flavour has an aroma of fresh orange.

- **Mouth feel**

Mouth feel is affected by the heat of solution of the soluble components (negative heat preferable), smoothness of the combination during chewing and hardness of the tablet. These factors are directly and almost entirely related to the active ingredient and major excipients. The term mouth feel is related to the type of sensation or touch that a tablet produces in the mouth upon chewing. It has nothing to do with chemical stimulation of olfactory nerves or taste buds. However, for a formulation to be successful, the overall effect in the mouth is important.

- **After effects**

The most common after effect of many compounds is after taste. For example, some iron salts have a rusty after taste; saccharin in high amounts tends to leave a bitter after taste. Another common after effect is a sensation of numbness of a portion or the whole surface of the tongue and mouth.

- **Flavouring**

The term flavour generally refers to a specific combined sensation of taste and smell (olfaction). Flavour is imparted in a chewable tablet formulation by the use of various synthetic and natural flavouring compounds. Flavours are available as either liquids or spray-dried, free-flowing, fine granules. Liquid flavour compounds can be added to dry granules obtained from wet granulation or to dry granulation blends as fine spray. Spray-dried flavour granules can also be added directly to dry granules obtained from wet granulation or to direct compression blends.

- **Colouring**

For aesthetic appeal and product differentiation, chewable tablets are often coloured. Colorants can also be used to mask unappealing natural colour, resulting from various raw materials. Colorants can be used for the uniform production of batches if raw materials have a slightly different colour. Colorants in chewable tablets are usually chosen to match the flavour. Colorants are available as natural pigments and synthetic organic dyes. In chewable tablets, the most widely used forms of the colorant are aqueous soluble dyes and lakes made from these dyes.

- **Chewability**

Acceptability of chewable dosage forms also depends on the chewability of the product. Chewability of a chewable dosage form may be defined as effortless chewing of the product with no desirable gumminess, stickiness, chalkiness or grittiness, yet coupled with a pleasant cooling sensation in the mouth. These properties are imparted by the use of excipients that have inherently good mouth feel and chewability characteristics. Excipients with such properties include mannitol and blends of mannitol, sorbitol, fructose and sucrose.

1.6.3 Evaluation

- Physical examination
- Hardness
- Friability
- Dosage uniformity
- Disintegration
- Assay for drug content
- Dissolution
- Consumer acceptance simulation testing

1.6.4 Stability Testing [6]

Stability testing of dosage forms or drug products is carried out to evaluate time dependent changes, if any occurring within the dosage forms. Stability testing may be either accelerated or real time under ambient conditions. Accelerated storage conditions include high temperatures, high relative humidity and high light intensities. The stability testing of chewable tablets would include the following test:

- Active drug content determination.
- Changes in physical characteristics of the tablets.
- Changes in tablet hardness, friability, dissolution rate/extent of dissolution and increase in disintegration time.
- Moisture content of tablets.
- Stability of tablet taste-masking system.

1.6.5 Special problems encountered with Chewable Tablets

Due to the particular attributes, chewable tablets present several special difficulties with respect to the formulation, manufacture, packaging and evaluation.

- **Formulation**

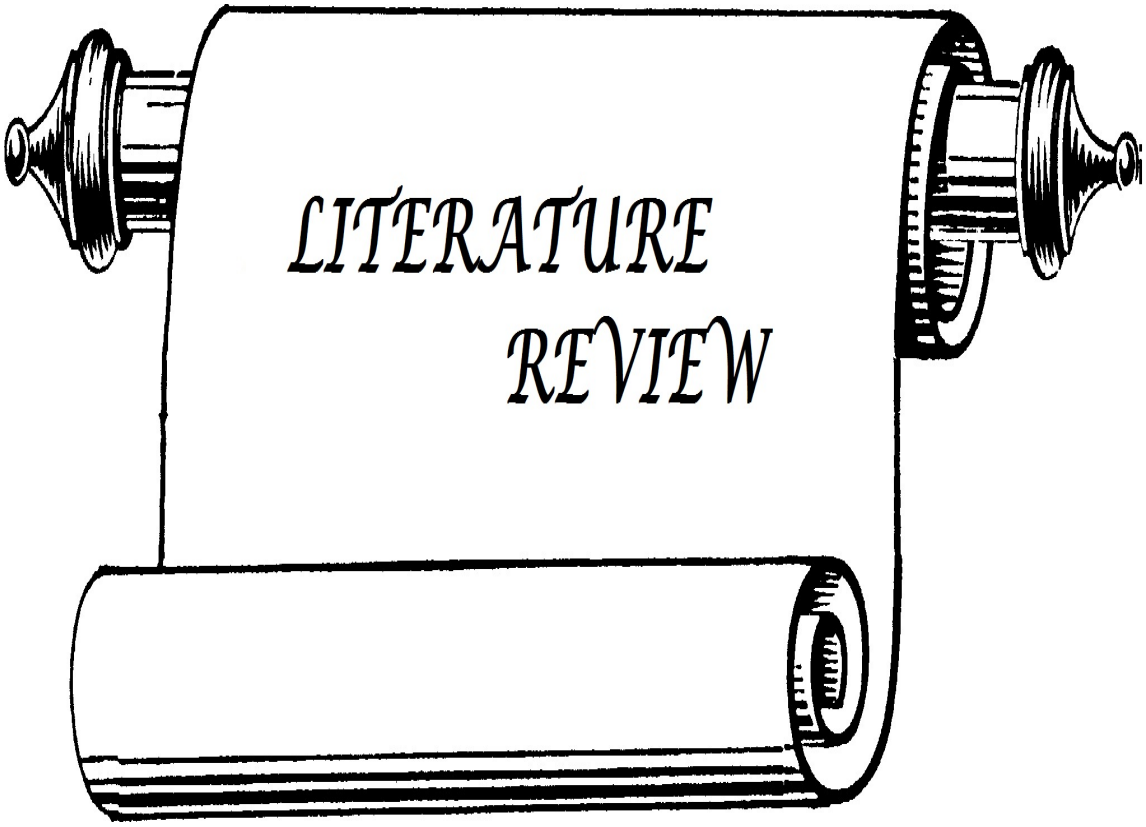
The associated attributes of a pleasant taste with matching colour, smoothness, mouth feel and chewability carry with them unusual formulation requirements compared to the tablets intended to be swallowed. The challenge of converting usually bad tasting (bitter, acidic or chalky) drugs into pharmaceutically elegant, good tasting dosage forms requires the application of highly specialized formulation skill. Flavour selection demands care in determining whether to mask or enhance the taste of the drug. Additionally, flavours should rarely be used singly; rather flavour blends can be used. Colour incorporation in chewable tablet formulation may be either by the use of dyes in wet granulation or by the use of lakes in direct compression or as additions to wet granulated materials after drying. The use of light or pastel colours in low concentration appropriately incorporated is critical to the overall appearance and acceptability of the product. Formulating for smoothness and mouth feel involves not only judicious excipient selection but also careful process development in establishing such parameters such as particle size, moisture content and compressional force. The importance of tablet hardness and friability cannot be over emphasized; minor changes in these variables may result in significant differences in perceived satisfaction during chewing. The tablets must be hard enough for machine handling, soft enough to be bitten easily, hard enough to provide acceptable consistency, soft enough to be chewed, hard enough not to feel powdery and soft enough to be smooth.

❖ **Manufacturing**

The four important aspects of chewable tablet manufacture related to the following:

- Proper incorporation of colouring agent.
- Assurance of necessary particle size distribution.
- Maintenance of correct moisture content.
- Achievement of proper tablet hardness.

The method and timing for the addition of flavour and colour must be determined if wet granulation is being used. Because most flavour substances are volatile, they cannot be subjected to elevated temperature. For this reason, they cannot be incorporated prior to wet granulation; rather flavours are added in the final blending operation of the process. The colour in the form of lake would be incorporated in the same step.


LITERATURE
REVIEW

2. LITERATURE REVIEW

2.1 Literature Review for Chewable Tablets

- **Swati Jagdale et al.**[8] formulated the chewable tablets of levimasole to overcome the difficulty in swallowing for paediatric and geriatric patients. Chewable tablets were prepared by using lactose or mannitol along with sodium starch glycolate in varying concentrations. Sodium saccharin and vanilla were used as sweetening agent and flavouring agent respectively. From the disintegration studies, it was observed that the formulation having no or less concentration of sodium starch glycolate shows increase in disintegration time. It was observed that the formulation containing lactose shows less disintegration time than formulation containing mannitol.
- **Hiroyuki Suzuki et al.**[9] developed an oral acetaminophen chewable tablets with inhibited bitter taste. Various formulations were developed using corn starch/lactose, cacao butter and hard fat (Witepsol H-15) as matrix bases and sucrose, cocoa powder and Benecoat BMI-40 as corrigents against bitter taste. The bitter taste intensity was evaluated using volunteers by comparison of test samples with standard solutions containing quinine at various concentrations. As a result the tablets made of Witepsol H-15/Benecoat BMI-40/sucrose, of Witepsol H-15/cocoa powder/sucrose and of Witepsol H-15/sucrose best masked the bitter taste so that they were tolerable enough to chew and swallow. The dosage forms masked the bitter taste well and showed good drug release indicating little change in bioavailability by masking.
- **Kathiresan K et al.**[10] formulated the loratadine chewable tablet 5mg to improve the patient acceptance in children. In this, five batches of loratidine tablets were formulated and evaluated. Various parameters like thickness, weight variation, friability, hardness, content uniformity of all formulations were studied. In *invitro* dissolution study, formulation 5 showed comparable release with innovator. Three month stability study of formulation 5 showed that there was no significant change in physical parameters, drug content and dissolution profile. So this study concluded that formulation 5 containing Avicel CE 15 and starch paste showed better characteristics than all other formulations.
- **Michele et al.**[11] studied the safety of chewable tablets in paediatric age group. Various informations on chewable tablets was performed from Jan 1996-Jan 1999 by evaluating various factors such as drug formulation, aspiration, choking, airway obstruction and foreign body. Additional information was obtained from the Physician's

desk reference, IMS Health National Prescription Audit Plus. The results of this study showed that more than 60 chewable tablet formulations are approved for use in United States of America. The advantages of chewable tablets include palatability, stability, precise dosing, portability and ease of delivery. From the available literature suggests that chewable were safe, well tolerated alternative to traditional paediatric drug formulations and offer significant advantages in children 2 years of age and older.

- **Hiraku Onishi et al.**[12] developed acetaminophen chewable tablets with suppressed bitterness and improved oral feeling by examination of hard fats as the matrix base and of sweetening agents as corrigents. Witepsol H-15, W-35, S-55, E-75, E-85 and Witocan H/ Witocan 42/44 were used for improved oral feeling. Sucrose, xylitol, saccharin, saccharin sodium, aspartame and sucralose were used as sweetening agents and applied alone or with Benecoat BMI-40 or cocoa powder. As a result of this study it was concluded that Witocan H tablet with Sc1-B5 is suggested as the best acetaminophen chewable tablet, exhibiting suppressed bitterness, low sweetness, improved oral feeling and good drug release.
- **Matthew P Millarney et al.**[13] studied the powder flow compact mechanical properties of sucrose and three high-intensity sweeteners used in chewable tablets. Sucrose, acesulfame potassium, saccharin sodium and aspartame are common pharmaceutical sweeteners used in solid dosage forms. These sweeteners were evaluated to determine the particle size, shape and true density. Powder flow, cohesivity and other mechanical properties were measured. Among these sweeteners, sucrose and acesulfame potassium showed excellent flowability and marginal mechanical property whereas saccharin sodium and aspartame demonstrated poor flowability and superior compact strength than the other. The study concluded that the sweetener selection should be appropriate to the done according the tableting process.

- **Barbara Knorr et al.**[14] made a study on dose selection of montelukast for adults as well as children. For adults (above 15 years of age), a 10 mg film coated tablet (FCT) is available and for children a 5mg chewable tablet (CT) is available. The adult montelukast dose (10-mg FCT) was selected on the basis of classic dose-ranging studies as the lowest dose that produces maximal improvement in both measures of airway function and patient- reported outcomes in chronic asthma and in the attenuation of exercise-induced bronchoconstriction. The strategy used for the paediatric dose selection for montelukast

was based on the determination of a CT dose that would provide an overall systemic exposure to montelukast in children similar to that in adults who receive a 10-mg FCT dose. A 5 mg chewable tablet yielded a comparable single-dose area under the plasma concentration-time curve profile to that of the adult 10-mg FCT dose and therefore it was selected as the paediatric dose for children aged 6 to 14 years with asthma. Subsequently, 2 studies of efficacy and tolerability validated the choice of the 5-mg CT dose.

- **Patsalos PN et al.**[15] compared the efficacy and tolerability of chewable carbamazepine to conventional carbamazepine in patiens with epilepsy. Thirty patients were studied. Duration of epilepsy was 21-68 years (median 34 years). Conventional and chew tablets were given and their serum concentration is measured from time to time. As a result of study it was concluded that chew tabs were essentially equivalent to the conventional formulation in efficacy and tolerability. After 12 weeks treatment, 19 patients preferred the chewable formulation.
- **Gary M Landsberg et al.**[16] studied the effectiveness of fluoxetine chewable tablets in the treatment of canine separation anxiety (SA) signs such as excessive salivation, inappropriate defecation, vocalization and urination. The study was carried as multi-center, placebo controlled, double blind, randomized parallel- arm study with 208 client owned dogs diagnosed with SA. As a result of this study it was conclude that fluoxetine chewable tablets at 1-2mg/kg/day showed some efficacy in improving overall separation anxiety severity scores in dogs. Fluoxetine chewable tablets represent a viable therapy for a condition that veterinary behaviourists rank as the second most common canine behavioural disorder.
- **Thomas J Nolan et al.**[17] studied the efficacy of an ivermectin/pyrantel pamoate chewable formulation against the canine hookworms, uncinaria stenocephala and ancylostoma caninum. This combination is for monthly use as a heartworm preventative and for treatment and control of canine hookworms. The formulation was found to be effective against both species of hook worms in experimentally infected dogs. No adverse effects was observed in any dog during the study by this drug combination.

2.2 Literature Review for Ubidecarenone

- **Pushp R Nepal et al.**[18] formulated solid dispersion of Coenzyme Q10 using Poloxamer 407 and Aerosil 200 to enhance the solubility and dissolution of CoQ10. Solid dispersion of CoQ10 with poloxamer 407 in weight ratio 1:5 prepared by melting method

but it exhibited poor stability. Then solid dispersion of CoQ10, Poloxamer 407 and Aerosil 200 (colloidal silicon dioxide) in the weight ratio 1:5:6 was formulated which exhibited improved stability during one month stability test, also solid dispersion containing Aerosil 200 showed enhanced drug release as well as dissolution rate of CoQ10. From the study it was concluded that solid dispersion formulation of CoQ10 with poloxamer 407 and Aerosil 200 possess enhanced solubility and dissolution rate of CoQ10 with good flowability and cost effectiveness.

- **Kommuru TR et al.**[19] formulated a self emulsifying drug delivery systems (SEDDS) of Coenzyme Q10 and its bioavailability is compared with powder formulation of CoQ10. Four types of SEDDS were prepared using two oils (Myvacet9-45 and Captex-200), two emulsifiers (Labrafac CM-10 and Labrasol) and a cosurfactant (lauroglycol). In all the formulations the level of CoQ10 was fixed at 5.66% w/w of the vehicle and the formulations are evaluated by droplet size analysis and pseudo ternary phase diagrams were constructed to find out the efficient self-emulsification region. Then the optimized formulation containing Myvacet 9-45 (40%), Labrasol (50%) and lauroglycol (10%) was selected and its bioavailability is compared with powder formulation of CoQ10. SEDDS shown improved bioavailability than powder formulation.
- **Sun sang kwon et al.**[20] has done the preparation, characterization of Coenzyme Q10 loaded Poly (methyl methacrylate) nano particles by a new emulsification process based on microfluidization and solvent evaporation method. The mean diameter of nano particles was found out by dynamic light scattering and transmission electron microscopy. The size of the particles depend upon the surfactants used and the recycling number of the microfluidization process. By ^{1}H NMR analysis the drug loading is estimated and it is found out to be above 95%. CoQ10 at its melting point 48°C formed a crystal structure within the polymer matrix and it was confirmed by differential scanning calorimetry. From the study it was concluded that polymer nanoparticles can be utilized as an effective means to stabilize chemically unstable drugs as well as to solubilise poorly soluble drugs.
- **Ankola DD et al**[21] formulated potent oral nano particles of CoQ10 to improve its bioavailability for the treatment of hypertension. Biodegradable nanoparticulate formulations based on poly(lactide-co-gylcolide) (PLGA) were prepared by emulsion technique using quaternary ammonium salt didodecyldimethylammonium bromide (DMAB) as a stabilizer. The entrapment efficiency and the particle size was studied using 5- 30% loading (107–110 nm). However, 50% and 75% led to increase in particle size

with no appreciable changes in entrapment efficiency. Then the intestinal uptake of CoQ10 as a suspension in carboxymethylcellulose (CMC), a commercial formulation and the developed nano particulate formulation was studied comparatively. The results shown that the developed nanoparticulate formulation had improved efficacy at a 60% lowered dose as compared to CoQ10 suspension and superior efficacy than the commercial formulation at an equal dose.

- **Effat Sadat et al.**[22] formulated and evaluated CoQ10 loaded solid lipid nanoparticles (SLN) cream and done a comparison study between simple cream of CoQ10, solid lipid nanoparticle alone and CoQ10 loaded solid lipid nanoparticles. Solid lipid nanoparticles of CoQ10 were formulated using high pressure homogenization method. The best formulation of SLN dispersion consisted of 13% lipid (cetyl palmitate or stearic acid), 8% surfactant (tween 80) and water. Stability tests, particle size analysis, differential scanning calorimetry, transmission electron microscopy and release study were conducted to find the best formulation. . In vitro release profiles of CoQ10 from simple cream, SLN alone, and CoQ10-loaded SLN cream showed prolonged release for SLNs compared with the simple cream, whereas there was no significant difference between SLN alone and SLN in cream. In vitro release studies also demonstrated that CoQ10-loaded SLN and SLN cream possessed a biphasic release pattern in comparison with simple cream. In vivo skin hydration and elasticity studies on 25 volunteers suggested good dermal penetration and useful activity of CoQ10 on skin as a hydrant and antiwrinkle cream.
- **Weis M et al.**[23] has carried out the comparitive study for bioavailability of four oral Coenzyme Q10-over trial. The included formulations were: a hard gelatin capsule containing 100 mg of CoQ and 400mg of Emcompress. Three soft gelatin capsules containing : 100mg of CoQ with 400mg of soy bean oil (Bioquinon); 100mg of CoQ with 20mg of polysorbate 80, 100mg of lecithin and 280mg of soy bean oil; and 100mg of CoQ with 20mg of polysorbate 80 and 380mg of soybean oil respectively. The result suggests that the soya bean oil suspension of CoQ has highest bioavailability.
- **Junya Hatanaka et al.**[24] studied the physicochemical and pharmacokinetic characterization of water soluble Coenzyme Q10 formulations. In this investigation, a nano emulsion (NE) and water soluble powder formulations including cyclodextrin-Q10 (CoQ10-CD) and dry emulsion (DE) were prepared and its physicochemical properties were characterized by dynamic light scattering, scanning electron microscopy, powder X-ray diffractometry and differential scanning calorimetry. Based on the results from

physicochemical characterization, CoQ10-loaded NE systems exhibited negatively charged and highly stable dispersion with submicron diameter when they were dispersed in water. In DE systems, CoQ10 existed mainly as an amorphous form, and this could be attributed to the higher solubility and dispersibility as compared to the crystalline form. Considering significant increment of both C_{max} and AUC of CoQ10, NE methodology could be the most effective among all formulations tested for the improvement of oral absorption of CoQ10.

- **Pariya Thanatuksorn et al.**[25] formulated CoQ10 with fats and emulsifiers to improve the bioavailability of CoQ10 and it was compared with that of a standard commercial product. Five commonly used fats (olive oil, safflower oil, coconut oil, butter and cocoa butter) four types of emulsifier (lecithin, monoglycerids, calcium stearoyo-2-lactate (CSL) and diacetyl tartaric acid esters of monoglycerides and two types of aqueous phase (distilled water with or without 8g/100g w/w skim milk). From the results it was found that oral bioavailability of the emulsified product was slightly greater than that of as standard commercial product.
- **Sarah Molyneux et al.**[26] studied the concentration response to the Coenzyme Q10 supplement Q-gel in human volunteers to identify the most effective dose Q-gel for use in supplementation studies. In this randomized cross over design, 8 young healthy male volunteers involved and they received single doses of 60,150 and 300mg of CoQ10 via Q-gel soft gel capsules. Blood samples were collected and analyzed for CoQ10. As a result of this study it was concluded that most efficacious single dose of Q gel is 200 mg and higher absorption is obtained using multiple smaller capsules.
- **Ullmann U et al.**[27] has made the comparison of bioavailability of a new tablet grade Coenzyme Q10 formulation(all-Q) with CoQ10 (Q gel) softsules from Tishcon corporation and Q-sorb from Nature's Bounty. Twelve healthy male subjects participated in a randomized, three-period cross over bioequivalence study. To compare bioavailability various pharmacokinetic parameters such as plasma CoQ10, AUC, Cmax for all three formulations were studied. The bioequivalence test concluded that Q-gel and all Q were found to be having better bioavailability properties than Q-sorb. At the sametime all-Q and Q-gel were bioequivalent, but all-Q can be used in tablets but Q-gel should be used in soft gels.

- **Michael V Miles et al.**[28] compared the bioavailability of Coenzyme Q10 from the over-the-counter supplements which are solubilized and non-solubilized in nature. The product A (LiQ-10), B(Q-Nol) and the reference product C (UbiQ gel) were given to nine healthy adults in single 180 mg doses of each Coenzyme Q10 formulation at two week intervals. ANOVA comparison for maximum plasma concentrations (C_{max}), time of maximum concentrations (t_{max}), areas under the concentration (AUC) were done. The results of this study showed that LiQ-10 has increased bioequivalence compared to the reference product but did not reach statistical significance. Q-Nol has increased bioavailability compared to the reference product.
- **Choi CH et al.**[29] has studied the relative bioavailability of Coenzyme Q10 emulsion and three liposome formulations after a single oral administration (60mg/kg) into rats.

Emulsion was prepared using phospholipon 85G as emulsifier and three liposome formulations (neutral, anionic and cationic) were prepared by thin film hydration technique using phospholipon 85G, cholesterol and charge carrier lipids. Bioavailability of CoQ10 in emulsion was 1.5 to 2.6 fold greater than liposome formulations in terms of AUC and tmax was 3h for emulsion while for liposomes it was more than 6h. From the study it is suggested that bioavailability is a primary concern in selecting CoQ10 product especially when high plasma level is required in treatment of heart failure and parkinson's disease.

- **Karen M Smith et al.**[30] studied the dose ranging and efficacy study of high dose Coenzyme Q10 formulations in huntington's disease in R6/2 transgenic mouse model. CoQ10 resulted in a marked improvement in motor performance and grip strength, with reduction in weight loss, brain atrophy, and huntington inclusions in treated R6/2 mice. From the study it was demonstrated that high-dose administration of CoQ10 exerts a greater therapeutic benefit in a dose dependent manner in R6/2 mice than previously reported and suggest that clinical trials using high dose CoQ10 in Huntington Disease patients are warranted.
- **Terao K et al.**[31] studied the enhancement of oral bioavailability of Coenzyme Q10 by complexation with cyclodextrin in healthy adults. In this study bioavailability of CoQ10 with microcrystalline cellulose (CoQ10-MCC) is compared with cyclodextrin(CoQ10-CD) in twenty two volunteers. Single dose of 150mg capsule containing 30mg of CoQ10 were given and plasma levels of CoQ10 were determined by HPLC technique. From this study it is concluded that the oral absorption and bioavailability of CoQ10 in healthy adult

volunteers could be significantly enhanced by complexation with cyclodextrin, suggesting the potential use of cyclodextrin as formulation aid for orally administered CoQ10.

- **Abdel-azim et al.**[32] has done investigation to compare the bioavailability of three Coenzyme Q10 formulations in dogs using an open, randomized, multiple-dose cross over design. The formulations included a powder filled capsule (A,control) and two soft gelatin formulations (Q gel as water miscible of CoQ10,B and Q-Nol as the water miscible form of ubiquinol, the redudced form of CoQ10,C). Blood samples were collected for 72hr and plasma CoQ10 concentrations were determined by HPLC. Various parameters like AUC, Cmax, Tmax were calculated and compared statistically. From the investigation it was concluded that soft gelatin capsules containing water miscible CoQ10 formulations B (Q gel) and C(Q-Nol) were superior to powder filled formulations with regard to their biopharmaceutical characteristics.
- **Jing Zhang et al.**[33] studied about the effects of the molecular weight (Mw) and concentration of trimethyl chitosan (TMC) on Coenzyme Q10-loaded liposomes coated with trimethyl chitosan in selenite induced cataract. Particle size distribution and zeta potential was studied by transmission electron microscopy (TEM) and the entrapment efficiency was investigated. Then the precorneal residence time was studied in comparison with control group. In conclusion, the physical properties and precorneal retention time of liposomes could be modified with TMC and ophthalmic instillation of Coenzyme Q10 is able to retard selenite-induced cataract formation.
- **Anna Rita Fetoni et al.**[34] compared the effectiveness of CoQ10 with water soluble Coenzyme Q10 formulation (Q-ter) in a guinea pig model in preventing the noise induced hearing loss. CoQ10 was given intraperitoneally 1 h before and once daily for 3 days after pure tone noise exposure (6 kHz for 1 h at 120 dB SPL). Functional and morphological studies were carried out to find out the signs of apoptosis. Treatments decreased active caspase 3 expression and the number of apoptotic cells, but animals injected with Q-ter showed a greater degree of activity in preventing apoptosis and thus in improving hearing. These data confirm that solubility of Coenzyme Q10 improves the ability of CoQ10 in preventing oxidative injuries that result from mitochondrial dysfunction.
- **Stephen T Sinatra** [35] studied about the Coenzyme Q10 supplementation in the management of congestive heart failure. CoQ10 adjunctive therapy results to improve the quality of life and decrease in the incidence of cardiac complications in congestive heart

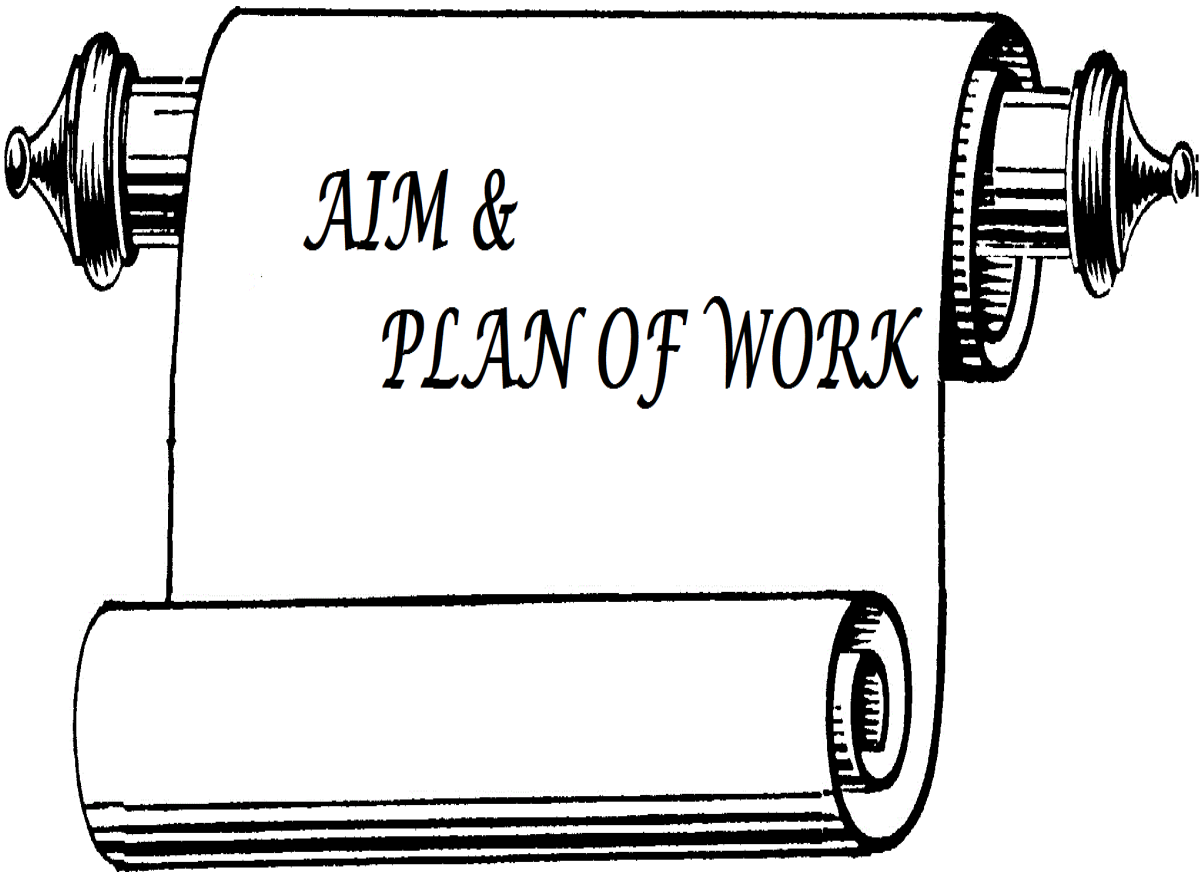
failure. But dosing, clinical application, bioavailability and dissolution of CoQ10 should be considered and based on that Q10 formulation should be supplemented to the patients.

- **Clifford W Shults et al.**[36] investigated about the safety and tolerability of high dosages of Coenzyme Q10 in 17 patients with Parkinson's disease. Escalating dosage of Coenzyme Q10 -1200,1800, 2400, 3400mg/day with a stable dosage of vitamin E 1200 IU/day was given and then plasma levels were noted. It was found that plasma level reached plateau at 2400mg /day and did not increase further at the 3000mg/day dosage. Thus from the study it was suggested that 2400mg/day is an appropriate highest dosage of CoQ10 to be given in Parkinson's disease.
- **Salvatore Pepe et al.**[37] made a review on role of Coenzyme Q10 in cardiovascular disease and given the following conclusions; 1.There is promising evidence of a beneficial effect of CoQ10 when given alone or in addition to standard therapies in hypertension and in heart failure, but less extensive evidence in ischemic heart disease. 2. Large scale multi-centre prospective randomised trials are indicated in all these areas but there are difficulties in funding such trials. 3. Presently, due to the notable absence of clinically significant side effects and likely therapeutic benefit, CoQ10 can be considered a safe adjunct to standard therapies in cardiovascular disease.

2.3 Literature Review for Excipients

- **Arnew Holzer and John Sjogren**[38] were studied the ability of sodium stearyl fumarate to reduce friction and adhesion to the punches and its influence on the tablet strength and disintegration time. The effect of lubricant concentration, particle size and mixing time was investigated using lactose and sodium chloride as tablet materials. Direct comparison of magnesium stearate with sodium stearyl fumarate was made. The friction and adhesion during ejection of tablets, disintegration time was studied and compared. As a result, it was concluded that Sodium stearyl fumarate was found to be a good alternative to magnesium stearate as a lubricant.
- **Rizk S et al.**[39] investigated the effect of lubricant on compression characteristics and drug dissolution rate of scleroglucan hydrophilic matrix. In this Sodium stearyl fumarate was compared to magnesium stearate and relationship between an increase in the polymer concentration and lubricant on compression behaviour and dissolution rate was studied. As a result, it was found that 0.5% of lubricant can influence both the compression ability and drug dissolution rate of scleroglucan hydrophilic matrix.

- **Jayadev Patil et al.**[40] worked on the formulation, design and evaluation of orally disintegrating tablets of loratidine using direct compression process. Loratidine tablets were formulated using suitable excipients like Maltodextrin, Mannitol, Micro crystalline cellulose, combination of Mannitol with starch, aspartame, croscarmellose sodium, citric acid, sodium bicarbonate along with Mint flavour. The tablets were evaluated for weight variation, hardness, friability, drug content, wetting time and disintegration time along with *invitro* dissolution. Finally it was concluded that the loratidine tablets formulated using commercial grades of excipients like combination of Mannitol with starch and Micro crystalline cellulose along with super disintegrants like croscarmellose sodium was found to be good.
- **Uday S Rangole et al.**[41] worked on formulation and *invitro* evaluation of rapidly disintegrating tablets by direct compression technology using hydrochlorthiazide as a model drug. Tablets were formulated using different concentration of superdisintegrants like croscarmellose sodium and crospovidone. Tablets were evaluated for disintegration time, wetting time, hardness, thickness, friability, uniformity of weight and dissolution study. As a result, it was found that crospovidone 4% gives disintegration in 16 sec and shows 100% drug release within 14 min is selected as the optimized formulation and its stability was found to be good for thirty days.
- **Ganesh Mahadev Chaulang et al.**[42] studied the effect of Crospovidone on physical properties and dissolution profile of tablets. From the study it was concluded that Crospovidone can be used for better dissolution of poorly soluble drugs like furosemide.


AIM &
PLAN OF WORK

3. AIM AND PLAN OF WORK

Aim

To formulate Ubidecarenone chewable tablet containing 400mg and to evaluate organoleptic characters such as taste and flavour along with *in vitro* release studies.

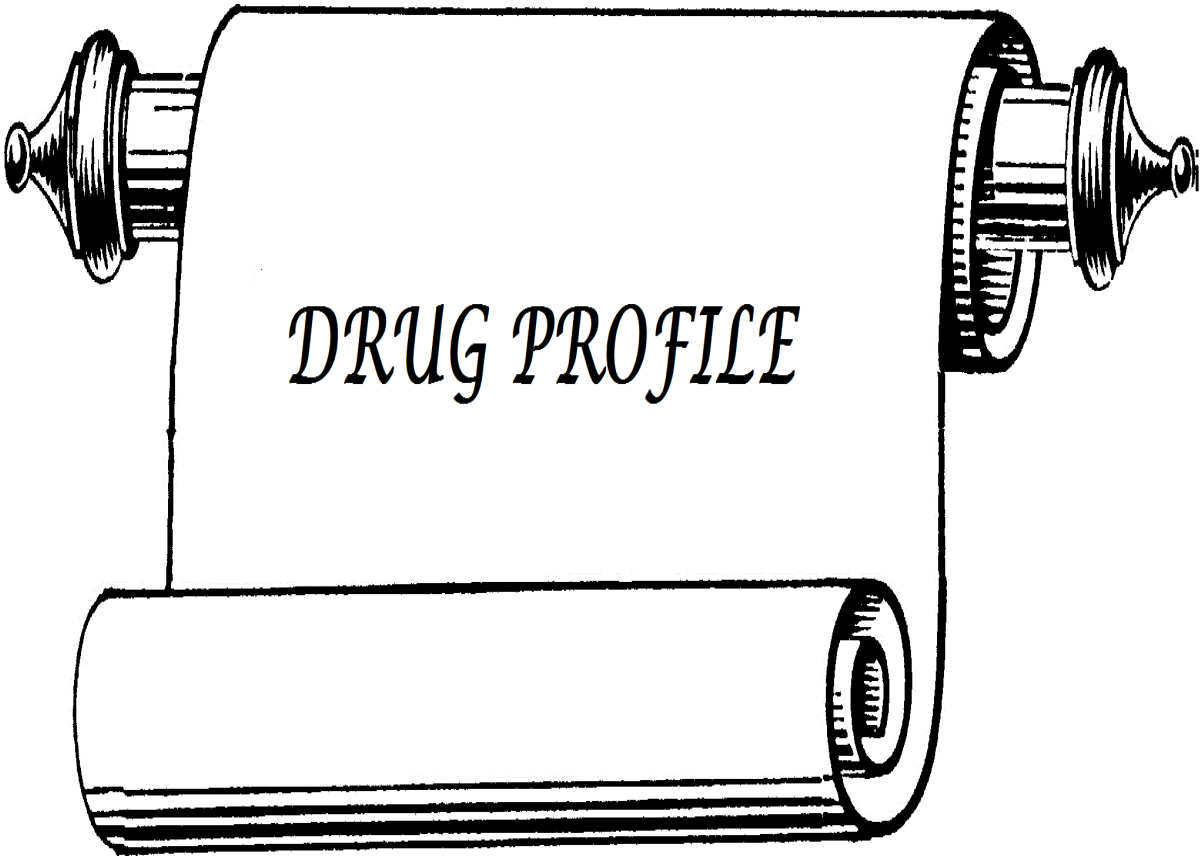
Plan of the work

- Pre-formulation studies
  - ✓ Drug- Excipent compatability studies
  - ✓ Assay
  - ✓ Water content
- In process Quality Control Checks for derived properties like Bulk Density, Tapped Density, Compressibility Index, Hausner's Ratio and Angle of Repose for drug and blends to be determined.
- Optimization of concentration of ingredients such as Flavours, Sweeteners, Disintegrant, Wetting agent, Glidant and Lubricant.
- Formulation of Chewable tablets with optimized ingredients.
- Evaluation of chewable tablets for post compression parameters like Uniformity of Weight, Thickness, Hardness, Friability, Disintegration Time, Assay and *in vitro* drug release characteristics to be studied.
- Palatability test has to be done for the optimized batch.
- Accelerated Stability Studies of the Ubidecarenone chewable tablets packed in 75 cc Amber coloured HDPE Bottle with 33 mm PP Child Resistant Cap with Induction sealed having 1 g of 6 g / yard cotton as dunnage, and 2 no's of 1 g Silica gel canister as desiccant; shall be determined at 40 ± 2°C / 75 ± 5% RH at one month interval for 3 months and the following are used as raiders for evaluation while comparing with Initial,
  - ✓ Appearance
  - ✓ Uniformity of weight
  - ✓ Thickness and Hardness
  - ✓ Disintegration Time
  - ✓ Water content
  - ✓ Assay
  - ✓ Dissolution studies

3. MARKETED FORMULATIONS OF UBIDECARENONE

Table No.2: Marketed formulations of Ubidecarenone

S.No	Brand Name	Strength	Dosage form	Manufacturer
1	CoQ10	10mg,30mg,50mg, 100mg,200mg, 300mg	Soft gels	Carlson labs, USA.
2	Coenzyme Q10	30mg, 100mg, 200mg, 400mg	Soft gels	Natural factors, Canada.
3	Coenzyme Q10	50mg	Soft gels	Roex, USA.
4	Coenzyme Q10 Sublingual	30mg, 60mg	Tablets	Source naturals, USA.
5	CoenzymeQ10 (emulsified with lecithin soya)	200mg	Soft gels	Douglas laboratories, USA.
6	CoQ10	100mg	Soft gels	Zenith Nutritions, India.
7	Ubi Q	30mg	Soft gels	Fourrts India Ltd, India.


DRUG PROFILE

5. DRUG PROFILE OF UBIDECARENONE[43]

Drug name : Ubidecarenone

Synonym : Coenzyme Q10

CAS NO : 303-98-0

Formula : $C_{59}H_{90}O_4$

Molecular weight : 863.34

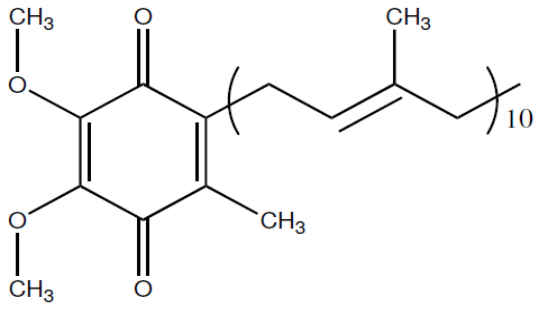
Physical form : yellow to orange crystalline powder

Odour : characteristic

Taste : bland taste

Melting point : 48ºC

Structure :



Chemical Name : 2,3-Dimethoxy-5-Methyl-6-Decaprenyl benzoquinone

Solubility : Practically insoluble in water, soluble in acetone, very slightly soluble in ethanol.

5.1 PHARMACOLOGY [44, 45]

5.1.1 Pharmacodynamics

The primary role of Ubidecarenone is as a vital intermediate of the electron transport system in the mitochondria. Adequate amounts of Ubidecarenone are necessary for cellular respiration and ATP production. Due to its involvement in ATP synthesis, Ubidecarenone affects the function of all cells in the body, making it essential for the health of all tissues and organs. Ubidecarenone also functions as an intercellular antioxidant at the mitochondrial level, perhaps accounting for its benefit in neurodegenerative diseases, male infertility and periodontal disease.

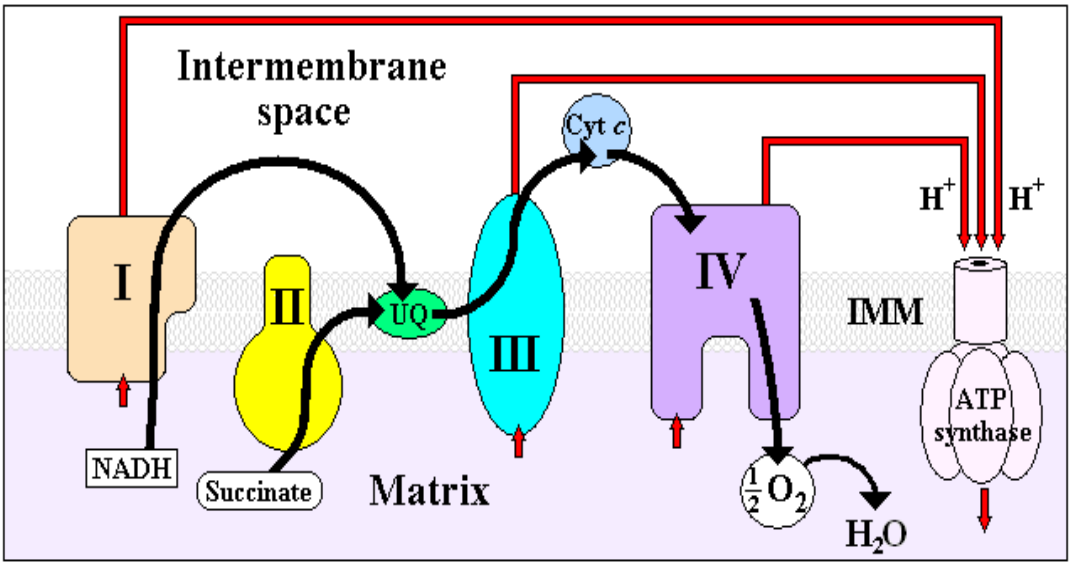


Fig 2: Electron Transport Chain

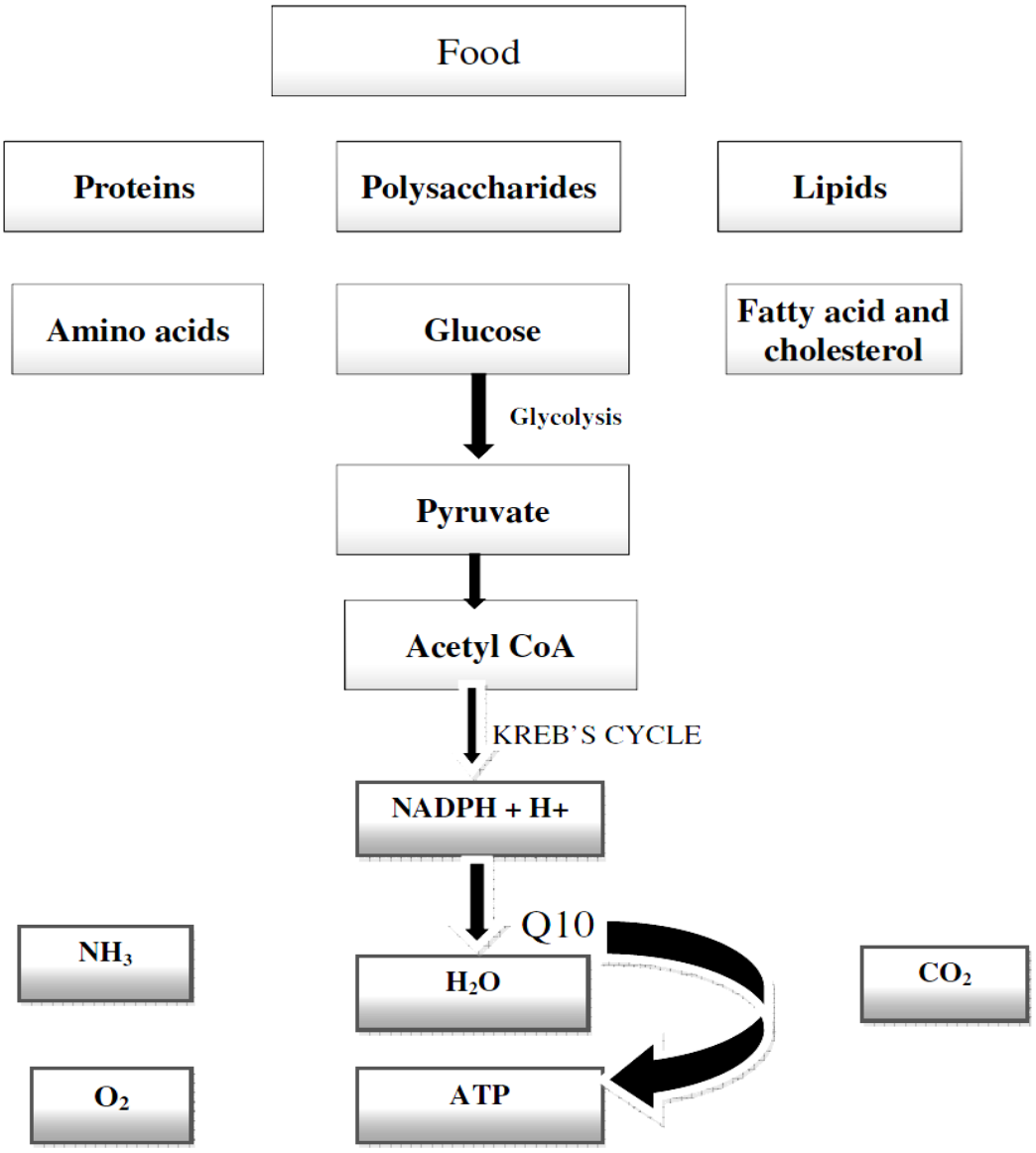


Fig 3: Role of Ubidecarenone in Energy Production

5.1.2 Pharmacokinetics [46]

ABSORPTION

- Ubidecarenone is absorbed from the small intestine, passes into the lymphatics, and finally to the blood and tissues.
- The absorption of Ubidecarenone is enhanced in the presence of lipids.
- Secretions from the pancreas and bile facilitate emulsification and micelle formation that is required for the absorption of fats.
- About 95% of Ubidecarenone in circulation exists in its reduced form as ubiquinol in human.
- Ubidecarenone absorption and bioavailability varies greatly depending on the type of Ubidecarenone formulation**.**

DISTRIBUTION

- Ubidecarenone level in body is estimated to be approximately 0.5–1.5 g in a normal adult.
- Sub cellular distribution of Ubidecarenone show a large portion (40–50%) of Ubidecarenone localized in the mitochondrial inner membrane, with smaller amounts in the other organelles also in the cytosol.
  - ***T_{max} 6 hours.***
  - ***$t_{1/2}$ 33 hours.***

METABOLISM AND EXCRETION

- Absorbed intact via the lymphatics and concentrated mainly in the liver.
- Excreted via the bile.
- Main metabolite was presumed to be a glucuronide of Q acid I [2, 3 dimethoxy-5-methyl-6-(30-methyl-50-carboxy-2-pentenyl)-1, 4-benzohydroquinone] formed in the liver.

5.1.3 ADVERSE EFFECTS [47]

- Diarrhoea.
- Loss of appetite.
- Nausea.
- Stomach upset.
- Trouble sleeping.
- Severe allergic reactions (rash, hives, itching, difficulty in breathing, tightness in the chest, swelling of the mouth, face, lips or tongue).

5.1.4 PRECAUTIONS

- Liquid forms, chewable tablets, dissolving forms of Ubidecarenone contain sugar, alcohol or aspartame. Patients having the history of diabetes, alcohol dependence, liver disease, Phenylketonuria (PKU) should take this medication with caution.
- During pregnancy, this drug should be used only when clearly needed.

5.1.5 DRUG INTERACTIONS

- **Chemotherapy medications**

  Ubidecarenone's anti oxidant effect might make some chemotherapy drugs less effective.

- **Daunorubicin and doxorubicin**

  Ubidecarenone may help to reduce the toxic effects on the heart caused by daunorubicin (cerubidin) and doxorubicin (Adiramycin).

- **Blood pressure medications**

  Ubidecarenone may work with blood pressure medications to lower blood pressure. In a clinical study of people taking blood pressure medications, adding Ubidecarenone supplements allowed them to lower the doses of these medications.

- **Blood thinning medications**

Ubidecarenone, when it is given Warfarin (Coumadin) or Clopidigrel (plavix) it reduces the blood thinning effect of blood.Ubidecarenone supplements when given with Betaxolol drops (Betoptic), a beta blocker medication used to treat glaucoma, it reduces heart related side effects.

Other medications that can lower the level of Ubidecarenone in the body include

- Statins for cholesterol, including Atorvastatin (lipitor), Lovastatin (Mevacor), Pravastatin (Pravachol) and Simvastatin (Zocor).
- Beta-blockers for high blood pressure, such as Atenolol (Tenormin), Labetolol (Normodyne), Metoprolol (Lopressor or toprol) and Propranolol (Inderal).
- Tricyclic antidepressant medications, including Amitriptyline (Elavil), Doxepin (Sinequan) and Imipramine (Tofranil).

5.1.6 DOSAGE INFORMATION [44]

- For most disease and other neurological conditions found doses ranging from 400 to 1200mg daily in divided doses.
- For breast cancer **390mg** daily.
- For Parkinson's disease doses ranging from **400-1200mg** daily to be effective.
- For cardiovascular disease dosages range from 100 to 200mg/day.
- Dosages of upto 15mg/kg/day are being employed in the case of mitochondrial cytopathy patients.

5.1.7 TOXICITY

Ubidecarenone appears to be quite safe, even at the highest doses cited in the literature. Occasional reports of nausea, anorexia or skin eruptions have been reported with Ubidecarenone supplementation.

5.1.8 USES [45, 48]

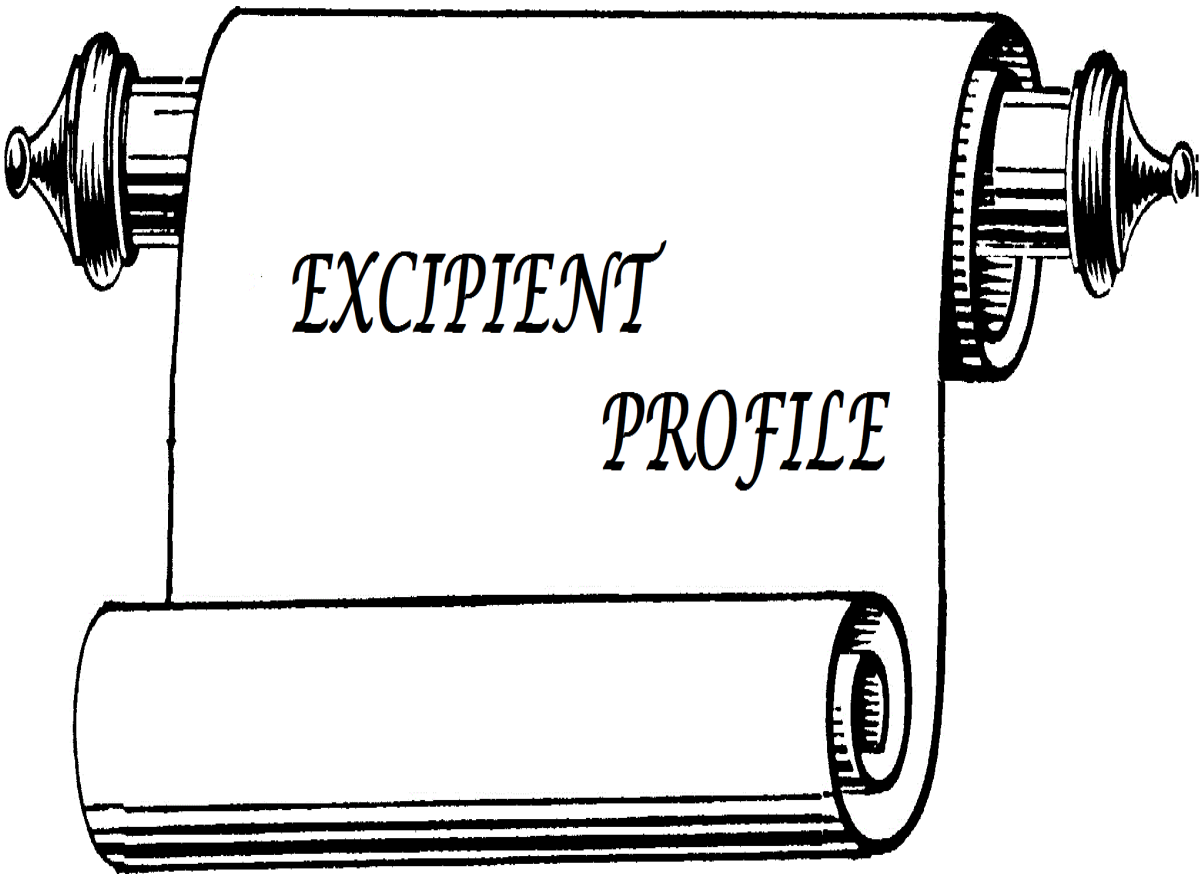
Ubidecarenone supplements, either by themselves or in with other drug therapies, may help to prevent or treat the following conditions:

- After Heart Attack.
- Heart failure (HF).
- Hypertension.
- Hyperlipidemia.
- Diabetes.

- Heart damage caused by chemotherapy.
- Heart surgery.
- Gum (Periodontal) disease.

Preliminary clinical studies also suggest that Ubidecarenone may:

- Improve immune function in people with HIV or AIDS.
- Increase sperm motility, improving male fertility.
- Used as part of the treatment for Parkinson's disease.
- Improve exercise ability in people with angina.
- Helps to prevent migraines.


EXCIPIENT
PROFILE

6. EXCIPIENT PROFILE

6.1 MANNITOL[49]

6.1.1. Non proprietary Names

BP : Mannitol

JP : D-Mannitol

PhEur : Mannitol

USP-NF : Mannitol

6.1.2. Synonyms

Cordycepic acid, E421, Emprove, manna sugar, D-mannite, mannite, mannitolum, Mannogem, Pearlitol.

6.1.3. Functional Category

Sweetening agent, tablet and capsule diluent, tonicity agent, vehicle (bulking agent) for lyophilized preparations.

6.1.4. Description

Mannitol is D-mannitol. It is a hexahydric alcohol related to mannose and is isomeric with sorbitol. Mannitol occurs as a white, odourless, crystalline powder or free-flowing granules. It has a sweet taste, approximately as sweet as glucose and half as sweet as sucrose, and imparts a cooling sensation in the mouth.

6.1.5. Chemical Name : D-Mannitol

6.1.6. Empirical Formula : $C_6H_{14}O_6$

6.1.7. Molecular Weight : 182.17

6.1.8. Applications in Pharmaceutical Formulation or Technology

- Mannitol is widely used in pharmaceutical formulations and food products.
- In pharmaceutical preparations it is primarily used as a diluent (10–90% w/w) in tablet formulations.
- Mannitol is commonly used as an excipient in the manufacture of chewable tablet formulations because of its negative heat of solution, sweetness and 'mouth feel'.

6.1.9. Typical properties

Density (Bulk) : 0.430 g/cm^3 for powder

0.7 g/cm^3 for granules

Density (Tapped) : 0.734 g/cm^3 for powder
0.8 g/cm^3 for granules.

Density (True) : 1.514 g/cm^3

6.1.10. Stability and Storage Conditions

Mannitol is stable in the dry state and in aqueous solutions. In solution, mannitol is neither attacked by cold, dilute acids or alkalis, nor by atmospheric oxygen in the absence of catalysts. The bulk material should be stored in a well-closed container in a cool, dry place.

6.1.11. Incompatibilities

Mannitol solutions, 20% w/v or stronger, may be salted out by potassium chloride or sodium chloride.

6.1.12. Safety

After intravenous injection, mannitol is not metabolized to any appreciable extent and is minimally reabsorbed by the renal tubule, about 80% of a dose being excreted in the urine in 3 hours.

6.2 CROSPOVIDONE[49]

6.2.1. Non proprietary Names

BP : Crospovidone

PhEur : Crospovidone

USP-NF : Crospovidone

6.2.2. Synonyms

Crospovidonum, Crospopharm, crosslinked povidone, E1202, Kollidon CL, Kollidon CL-M, Polyplasdone XL, PolyplasdoneXL-10, polyvinylpolypyrrolidone, PVPP, 1-vinyl-2-pyrrolidinone homopolymer.

6.2.3. Functional category

Tablet disintegrant

6.2.4. Description

Crospovidone is a white to creamy white, finely divided, free flowing, practically tasteless, odourless or nearly odourless, hygroscopic powder.

6.2.5. Chemical name

1-Ethenyl-2-pyrrolidinone homo polymer

6.2.6. Empirical formula : $(C_6H_9NO)_n$

6.2.7. Molecular weight : >1 000000

6.2.8. Applications in Pharmaceutical Formulation or Technology

- Crospovidone is a water-insoluble tablet disintegrant and dissolution agent used at 2–5% concentration in tablets prepared by direct- compression or wet- and dry-granulation methods.
- Crospovidone can also be used as a solubility enhancer.

6.2.9. Typical properties

- Acidity/Alkalinity : pH= 5.0–8.0 (1% W/V Aqueous Slurry).
- Density : 1.22 g/cm^3

6.2.10. Stability and storage conditions

Since Crospovidone is hygroscopic, it should be stored in an airtight container in a cool, dry place.

6.2.11. Incompatibilities

- Crospovidone is compatible with most organic and inorganic pharmaceutical ingredients.
- It is when exposed to high water level forms a molecular adducts with some materials.

6.2.12. Safety

- Crospovidone is non toxic and non irritant material.
- No adverse effects associated with Crospovidone.

6.3 POLOXAMER 407[49]

6.3.1. Non proprietary Names

BP : Poloxamers

PhEur : Poloxamers

USP-NF : Poloxamer

6.3.2. Synonyms

Lutrol, pluronic, poloxalkol

6.3.3. Functional Category

Dispersing agent, emulsifying agent, solubilising agent, tablet lubricant, wetting agent.

6.3.4. Description

Poloxamers generally occurs as white, waxy, free flowing prilled granules or as cast solids. They are practically odourless and tasteless.

6.3.5. Chemical name

α-Hydro-o-hydroxypoly(oxyethylene)poly(oxypropylene) poly- (oxyethylene) block copolymer.

6.3.6. Applications in Pharmaceutical Formulation or Technology

- Poloxamer 188 is used as a wetting agent, stool lubricant in constipation.
- Poloxamers may be used as wetting agents in eye drop formulations, in the treatment of kidney stones and as a skin wound cleansers.
- Poloxamer 338 and 407 are used in solutions for contact lens care.

Table No. 3: Applications of Poloxamer

Uses of poloxamer	
Use	**Concentration (%)**
Fat emulsifier	0.3
Flavour emulsifier	0.3
Fluorocarbon emulsifier	2.5
Gelling agent	15-50
Spreading agent	1
Stabilizing agent	1-5
Tablet coating	10
Tablet excipient	5-10
Wetting agent	0.01-5

6.3.7. Typical properties

Acidity /alkalinity : pH =5.0-7.4 for a 2.5% w/v aqueous solution

Density : 1.06 g/cm^3 at 258ºC

6.3.8. Stability and storage conditions

- Poloxamers are stable materials.
- Aqueous solutions are stable in acids, alkalis and metal ions but it support mold growth.
- The bulk material should be stored in a well closed container in a cool dry place.

6.3.9. Incompatibilities

Depending on the relative concentrations, Poloxamer 188 is incompatible with Phenols and Parabens.

6.3.10. Safety

- Poloxamers are generally regarded as non toxic and non irritant material.
- Poloxamers are not metabolized in the body.

6.4 SACCHARIN SODIUM[49]

6.4.1. Non proprietary Names

BP : Saccharin Sodium

JP : Saccharin Sodium Hydrate

PhEur : Saccharin Sodium

USP-NF : Saccharin Sodium

6.4.2. Synonyms

1,2-Benzisothiazolin-3-one 1,1-dioxide, sodium salt, sodium benzosulfimide, soluble gluside, soluble saccharin, sucaryl Sodium.

6.4.3 Functional category : Sweetening agent

6.4.4. Description

Saccharin sodium occurs as a white, odourless or faintly aromatic, efflorescent, crystalline powder. It has an intensely sweet taste, with a metallic aftertaste.

6.4.5. Chemical Name : 1,2-Benzisothiazol-3(2H)-one 1,1-dioxide, sodium salt.

6.4.6. Empirical Formula : $C_7H_4NNaO_3S$

6.4.7. Molecular Weight : 205.16

6.4.8. Functional Category : Sweetening agent

6.4.9. Applications in Pharmaceutical Formulation or Technology

- Saccharin sodium is an intense sweetening agent used in beverages, food products, and pharmaceutical formulations such as tablets, powders, medicated confectionery, gels, suspensions, liquids, and mouthwashes. It is also used in vitamin preparations.
- Saccharin sodium enhances flavour systems and may be used to mask some unpleasant taste characteristics.

6.4.10. Stability and Storage Conditions

- Saccharin sodium is stable under the normal range of conditions employed in formulations.
- Saccharin sodium should be stored in a well-closed container in a cool, dry place.

6.4.11. Incompatibilities : None

6.4.12. Safety : It is regarded as a safe, intense sweetener.

6.5 ASPARTAME[49]

6.5.1. Non proprietary Names

BP : Aspartame

PhEur : Aspartame

USP-NF : Aspartame

6.5.2. Synonyms

Canderel, E951, Equal, methyl N-L-phenylalaninate, Natra taste, Pal sweet diet, Sasnecta, SC-18862, Tri-sweet.

6.5.3. Description

Aspartame occurs as an off white, almost odourless crystalline powder with an intensely sweet taste.

6.5.4. Functional category : Sweetening agent

6.5.5. Empirical formula : $C_{14}H_{18}N_2O_5$

6.5.6. Molecular weight : 294.30

6.5.7. Applications in pharmaceutical technology

- Aspartame is used as an intense sweetening agent in beverage products, food products and table top sweeteners tablets and other preparations.
- It enhances flavour and masks the unpleasant taste characteristics, its sweetening power is 180-200 times that of sucrose.

6.5.8. Typical properties

Acidity/alkalinity : pH 4.5-6.0 (0.8% w/v aqueous solution)

Density (bulk) : 0.5-0.7 g/cm^3 for granular grade

: 0.2-0.4 g/cm^3 for powder grade

: 0.29 g/cm^3 (tapped density)

6.5.9. Stability and storage conditions

- Aspartame is stable in dry conditions.
- In presence of moisture it undergoes hydrolysis and forms degradation products.

6.5.10. Incompatabilities

Aspartame is incompatible with dicalcium phosphate and magnesium stearate.

6.5.11. Safety

Aspartame is widely used in oral formulations as sweeteners but it undergoes metabolism and forms toxic by products like phenyl alanine, methanol and aspartic acid. So it is not recommended in patients with phenylketonuria. Other side effects on consumption of aspartame results in headaches, memory loss, gastrointestinal symptoms and dermatological symptoms.

6.6 COLLOIDAL SILICON DIOXIDE[49]

6.6.1. Nonproprietary Names

BP : Colloidal anhydrous silica

PhEur : Silica colloidalis anhydrica

USPNF : Colloidal silicon dioxide

6.6.2. Synonyms

Aerosil, Cab-O-Sil, colloidal silica, light anhydrous silicic acid, silicic anhydride, silicon dioxide fumed.

6.6.3. Description

It is a submicroscopic fumed silica with a particle size of about 15 nm. It is a light, loose, bluish-white-colored, odorless, tasteless, non-gritty amorphous powder.

6.6.4. Chemical Name : Silica

6.6.5. Empirical Formula : SiO_2

6.6.6. Molecular Weight : 60.08

6.6.7. Functional Category : Adsorbent, anti caking agent, glidant, tablet disintegrant, viscosity-increasing agent.

6.6.8. Applications in Pharmaceutical Formulation or Technology

- It is widely used in pharmaceuticals, cosmetics, and food products.
- Also used to stabilize emulsions and as a thixotropic thickening and suspending agent in gels and semisolid preparations.
- Also used as a tablet disintegrant and as an adsorbent, dispersing agent for liquids in powders.

6.6.9. Typical Properties

- Acidity/alkalinity pH = 3.8–4.2 (4% w/v aqueous dispersion)
- Density (bulk) 0.029–0.042 g/cm^3

6.6.10. Stability and Storage Conditions

- It is hygroscopic but adsorbs large quantities of water without liquefying.
- Colloidal silicon dioxide powder should be stored in a well-closed container.

6.6.11. Incompatibilities

Incompatible with diethylstilbosterol preparations.

6.6.12. Safety

Colloidal silicon dioxide is widely used in oral and topical pharmaceutical products and is generally regarded as an essentially non-toxic and non-irritant excipient.

6.7 SODIUM STEARYL FUMARATE[49]

6.7.1. Non-proprietary Names

BP : Sodium Stearyl Fumarate

PhEur : Sodium Stearyl Fumarate

USP-NF : Sodium Stearyl Fumarate

6.7.2. Synonyms

Fumaric acid, octadecyl ester, sodium salt; natrii stearylis fumaras; Pruv; sodium monostearyfumarate.

6.7.3 Description

Sodium stearyl fumarate is a fine, white powder with agglomerates of flat, circular-shaped particles.

6.7.4. Functional Category **:** Tablet and capsule lubricant.

6.7. 5. Chemical Name **:** 2-Butenedioic acimd, onooctadecyl ester, sodium salt

6.7.6. Empirical Formula : $C_{22}H_{39}NaO_4$

6.7.7. Molecular Weight : 390.5

6.7.8. Applications in Pharmaceutical Formulation or Technology

- Sodium stearyl fumarate is used as a lubricant in capsule and tablet formulations at 0.5–2.0% w/w concentration.
- It is also used in certain food applications.

6.7.9. Typical properties

Acidity/alkalinity : pH = 8.3 for a 5% w/v aqueous solution at 90ºC.

Density : 1.107 g/cm^3

Density (bulk) : 0.2–0.35 g/cm^3

Density (tapped : 0.3–0.5 g/cm^3

6.7.10. Stability and storage conditions

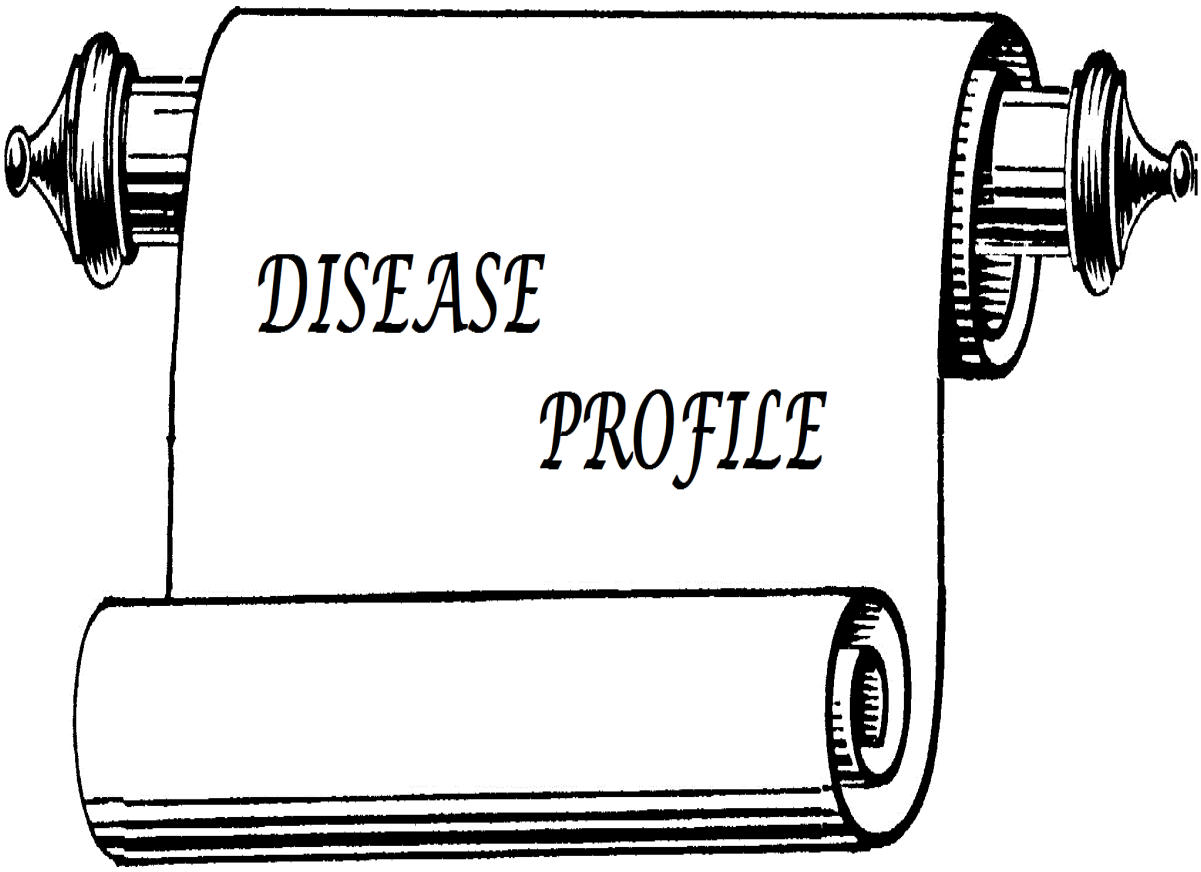
The bulk material should be stored in a well-closed container in a cool, dry place.

6.7.11. Incompatibilities

Sodium stearyl fumarate is reported to be incompatible with chlorhexidine acetate.

6.7.12. Safety

Sodium stearyl fumarate is used in oral pharmaceutical formulations and is generally regarded as a nontoxic and non-irritant material.


DISEASE
PROFILE

7. DISEASE PROFILE[44]

` Ubidecarenone is a compound found naturally in the human body. Because of its ubiquitous presence in nature and its quinone structure (similar to that of vitamin K), Ubidecarenone is also known as ubiquinone.

Tissue deficiencies or subnormal serum levels of Ubidecarenone have been reported in a wide range of medical conditions, including

- Cardiovascular disease.
- Neuromuscular disease.
- Mitochondrial disorders.
- Acquired Immune Deficiency Syndrome.
- Cancer.
- Migraine
- Thyroid Disorders.
- Periodontal Disease.
- Gastric Ulcer.
- Obesity.
- Asthma.
- Diabetes.
- Muscular dystrophy.
- Allergy.

7.1 CARDIOVASCULAR DISEASES

7.1.1 Hypertension[44]

Hypertension is the condition in which systolic blood pressure is above 140mm of Hg and diastolic pressure above 90mm of Hg. Epidemiological studies have confirmed that higher the blood pressure greater the risk of cardiovascular disease. Mechanism behind antihypertensive effect of Ubidecarenone is its ability to induce vasodilation via decreased peripheral resistance in the vasculature. Ubidecarenone's antioxidant properties results in quenching of free radicals that cause inactivation of endothelium-derived relaxing factor and/or fibrosis of arteriole smooth muscle.

7.1.2 Heart Failure [50]

Ubidecarenone has the promising beneficial effect in heart failure when it is given alone or along with standard therapies. Ubidecarenone improves the cardiovascular function by increasing energy production, increases contraction of cardiac muscle.

7.1.3 Other Cardiovascular diseases

Ubidecarenone is also useful in conditions like

- Cardiomyopathy.
- Angina.
- Arrhythmias.
- Acute myocardial infarction.

Ubidecarenone supplementation improves the cardiovascular function through the following mechanism,

- Enhanced energy production.
- Improved contractility of cardiac muscle.
- Potent antioxidant activity.
- Prevention of LDL oxidation.

7.1.4 Hyperlipidemia and Statin Drugs [51, 52]

Ubidecarenone is essential in mitochondrial respiration. HMG CoA reductase inhibitors used in the treatment of hyperlipidemia interfere with the production of mevalonic acid, which is a precursor in the synthesis of Ubidecarenone. This result in reduction of Ubidecarenone levels in serum which produces Rhabdomylosis. Thus Ubidecarenone supplement is essential in statin therapy.

7.2 NEUROLOGICAL CONDITIONS

7.2.1 Parkinson's Disease[53]

It is an extrapyramidal motor disorder characterized by rigidity, tremor and hypokinesia with secondary manifestations like defective posture, mask-like face, sialorrhoea, dysphagia and dementia. It is a degenerative neurological disorder for which no treatment has been shown to slow down the progression. Ubidecarenone appears to slow the progressive deterioration of function in Parkinson disease. Ubidecarenone play a role in the cellular dysfunction found in Parkinson's disease (PD), providing a protective agent for Parkinsonian patients.

7.2.2 Huntington's Disease

Huntington's disease (HD) is a progressive neurodegenerative disease characterized by abnormalities in mitochondrial morphology and activity. This condition is also treated by Ubidecarenone.

7.3 MITOCHONDRIAL DISORDERS[54]

Mitochondrial disorders occur due to deficiency of Ubidecarenone in the cells. Ubidecarenone deficiency has been associated with five major clinical phenotypes:

i) Encephalomyopathy
ii) Severe infantile multisystemic disease
iii) Cerebellar ataxia
iv) Isolated Myopathy
v) Nephritic syndrome.

Ubidecarenone supplementation typically in dosages from 30-300 mg daily is given to improve the mitochondrial disorders.

7.4 ACQUIRED IMMUNODEFICIENCY SYNDROME (AIDS) [55]

AIDS is a complex disease that is associated with a wide range of nutritional deficiencies and immunological disorders. Since oxidative stress is believed to be involved in the pathogenesis of AIDS-related diseases, the antioxidant activity of Ubidecarenone helps in preventing AIDS-related diseases such as cardiomyopathy and lipodystrophy that can be caused by oxidative stress. Blood levels of Ubidecarenone are lower in AIDS patients and supplementation with 200 mg/day has been shown to increase T4/T8 ratios in these individuals.

7.5 CANCER [56, 57]

Decreased levels of Ubidecarenone have been found in plasma of women with breast cancer and in cancerous breast tissue. Oxygen derived radicals are able to cause damage to membranes, mitochondria and macromolecules including proteins, lipids and DNA. Mechanisms for Ubidecarenone in cancer include immune system enhancement and antioxidant activity. 390 mg of Ubidecarenone daily results in tumor regression and disappearance of previously diagnosed metastasis. Ubidecarenone can be depleted by the use of the chemotherapeutic drug doxorubicin (Adriamycin®), resulting in cardiotoxicity if a high enough cumulative dose is achieved. Ubidecarenone is a potential anticancer agent and it reduces the risk of prostate cancer.

7.6 MIGRAINE [58]

Migraine is also due to the impaired energy metabolism in brains and this can be treated by Ubidecarenone. Ubidecarenone improves energy metabolism and the dose of 300mg/day improves the condition of migraine and it is well tolerated.

7.7 THYROID DISORDERS[44]

Decreased levels of Ubidecarenone was found in plasma and thyroid tissue of individuals with certain forms of hyperthyroidism. In Grave's disease, excessive thyroid hormone stimulation and subsequent activation of mitochondrial function results in subnormal Ubidecarenone concentrations and thus it can be treated with Ubidecarenone.

7.8 PERIODONTAL DISEASE

Periodontal disease affects about 60% of young adults and 90% of individuals over the age of 65. Although proper oral hygiene is helpful, many people suffer from intractable gingivitis, often requiring surgery and resulting in eventual loss of teeth. Healing and repair of periodontal tissues requires efficient energy production, which depends on an adequate supply of Ubidecarenone. Gingival biopsies revealed subnormal tissue levels of Ubidecarenone in 60% to 96% patients with periodontal disease and low levels of Ubidecarenone in leukocytes in 86% of cases. These findings indicate that periodontal disease is frequently associated with Ubidecarenone deficiency.

7.9 GASTRIC ULCER

Susceptibility to gastric ulceration is related to the balance between ulcer promoting factors (such as excessive gastric acidity and infection with Helicobacter pylori) and resistance factors (such as tissue integrity, production of protective mucus and repair mechanisms). Free-radical damage is one of the primary mechanisms by which external factors induce gastric injury and Peptic ulceration. Since, Ubidecarenone possesses antioxidant activity, it is capable of preventing ulceration by reducing the amount of free-radical damage. In addition, the production of protective mucus and the rapid cell turnover of gastric mucosa are highly energy dependent processes, which require the presence of adequate amounts of Ubidecarenone.

7.10 OBESITY

The Obesity is associated in some cases with impaired energy production. This abnormality may be in part genetically determined. Individuals with a family history of obesity have a 50% reduction in their thermogenic response to meals, suggesting the presence of an hereditary defect in energy output. Ubidecarenone is an essential cofactor for energy production, thus Ubidecarenone deficiency is a contributing factor for obesity.

7.11 MUSCULAR DYSTROPHY

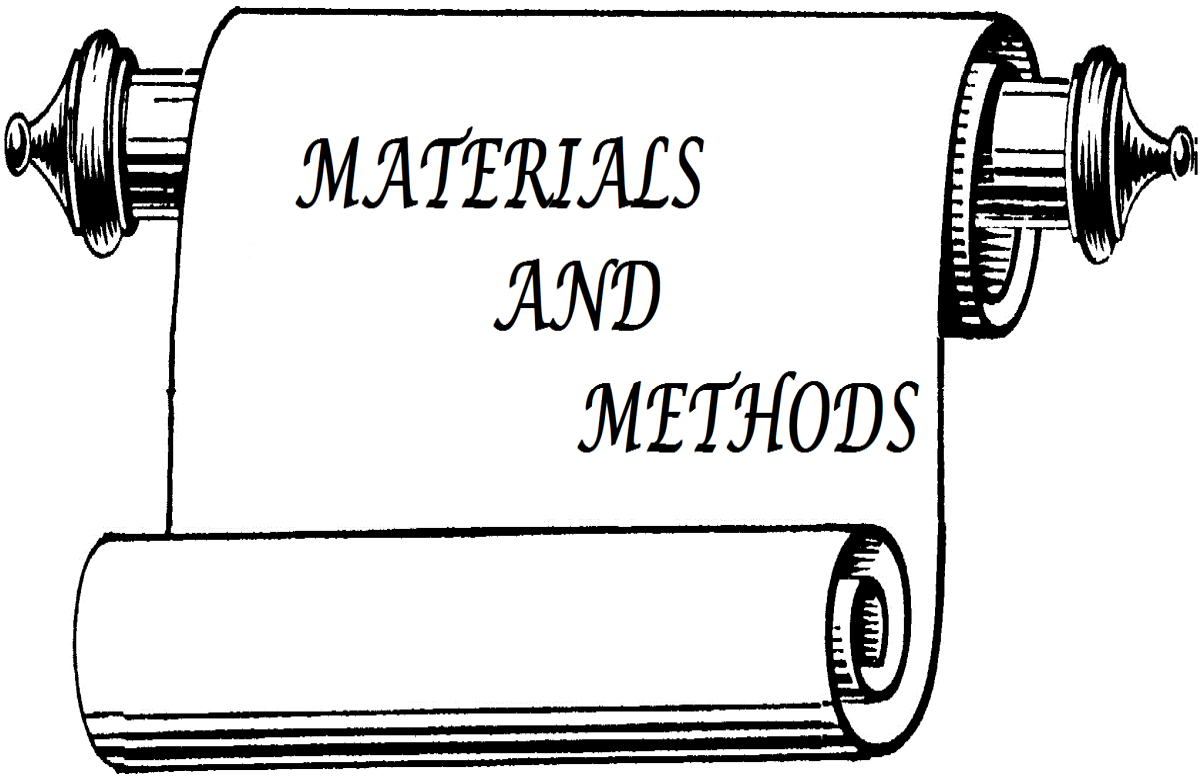
In muscular dystrophy, low levels of Ubidecarenone has been found in muscle mitochondria and it is involved in pathogenesis of cardiac disease, which occurs in virtually every form of muscular dystrophy and myopathy.

7.12 DIABETES

The electron-transport chain is integrally involved in carbohydrate metabolism. Serum Ubidecarenone levels in Type 2 diabetic patients are decreased and may be associated with subclinical diabetic cardiomyopathy and it is treated with Ubidecarenone supplementation.

7.13 ASTHMA

In case of asthma, low Ubidecarenone levels are found and it create oxidative stress and produces chronic mucosal inflammation. Thus Asthma can be treated with combination of corticosteroids and Ubidecarenone to give better effect.


MATERIALS
AND
METHODS

08. MATERIALS AND METHODS

Table No.4: LIST OF EQUIPMENTS

S.No	Instruments/Equipments	Manufacturer
1	Mixer with sigma blade	Lumix food processor
2	ASTM Sieve No 40(425µm)	Electro Pharma
3	ASTM Sieve No 60(250µm)	Electro Pharma
4	Moisture Analyzer	OHAUS MB 45
5	Tap density tester USP I	Electrolab ETD-1020
6	Friabilator USP	Electrolab EF-1W
7	Analytical balance	OHAUS adventurer
8	Top loading balance	Essae Teraoka Limited (model DS 450cw)
9	Disintegration tester USP	Electrolab ED-2L
10	16 station single Rotary compression machine	Cadmach , Ahmedabad, India
11	Hardness tester	Dr.Schleuniger Pharmatron model 5Y tablet tester
12	Vernier calliper	Mitutoyo
13	Dissolution Apparatus	Electrolab 8 Station (TDT - 08L)

Table no.5: LIST OF MATERIALS

S.No	Material	Manufacturer	Applications
1	Ubidecarenone	Sigma Aldrich, USA	API
2	Pearlitol flash (Mannitol with starch)	Roquette, France	Diluent
3	Saccharin Sodium	Nutrinova, Germany	Sweetener
4	Aspartame	Nutrinova, Germany	Sweetener
5	Mint flavour	Firmenich, Switzerland	Flavouring agent
6	Orange flavour	Firmenich, Switzerland	Flavouring agent
7	Crospovidone (Polyplasdone XL 10)	ISP Technologies, USA	Disintegrant
8	Poloxamer 407 (Lutrol Micro 127)	BASF, Germany	Wetting agent
9	Colloidal Silicon Dioxide (Cabosil)	Cabot Sanmar , USA	Glidant
10	Sodium Stearyl Fumarate (Pruv)	JRS Pharma, Germany	Lubricant

PREFORMULATION STUDIES

8.1 Drug - Excipient Compatibility Study [59]

The drug and excipients were taken in appropriate ratio and mixed well in a polybag and it was passed into 40 ASTM Sieve and then taken in 2ml glass vials (USP TYPE I). The filled vials were kept at 40 ± 2ºC/ 75 ± 5% RH and the samples withdrawn initially , 2nd week, 4th week and it was analyzed for the following,

- Appearance.
- Assay.
- Water content.

Table no.6: Drug– Excipient Compatibility Studies

S.No	Drug-Excipient	Ratio
1	Ubidecarenone – Pearlitol Flash	1:0.5
2	Ubidecarenone – Crospovidone	1:0.25
3	Ubidecarenone – Poloxamer 407	1:0.25
4	Ubidecarenone – Aspartame	1:0.25
5	Ubidecarenone – Saccharin Sodium	1:0.25
6	Ubidecarenone – Mint Flavour	1:0.25
7	Ubidecarenone – Orange Flavour	1:0.25
8	Ubidecarenone – Colloidal Silicon Dioxide	1:0.25
9	Ubidecarenone – Sodium Stearyl Fumarate	1:0.25

8.2 Particle size determination by sieving method [60]

Tare each test sieve to the nearest 0.1 g. The weight of the empty sieves were noted. The test sieves were stacked in the ascending order with sieve with largest aperture size on the top and the smallest in the bottom. Replace the lid. An accurately weighed sample of 25g was placed on the top of the sieve. The nest of sieves were agitated for 5 minutes automatically in mechanical shaker. Then the sieves were reassembled carefully and the weight of material retained on each sieve was determined. The particle size distribution of the raw material was then calculated.

8.3 Bulk Density (ρ_b)[61]

It is the ratio of total mass of powder to the bulk volume of powder. It was measured by pouring the weighed powder into a measuring cylinder. This initial volume was called the bulk volume. From this the bulk density was calculated according to the formula mentioned below. It is expressed in gm/mL and is given by

$$\rho_b = M/ V_b$$

Where, ρ_b – Bulk density (g/mL)

M - Mass of powder (g)

V_o - Bulk volume of the powder (mL).

8.4 Tapped Density (ρ_t) [61]

It was achieved by mechanically tapping a measuring cylinder containing a powder sample. After observing the initial volume, the cylinder was mechanically tapped and volume readings were taken until little further volume change was observed. The mechanical tapping was achieved by raising the cylinder and allowing it to drop under its own weight at a specific distance. Devices that rotate the cylinder during tapping may minimize any possible separation of the mass during tapping down. The tapped volume was measured by tapping the powder to constant volume. It is expressed in g/mL and is given by

$$\rho_t = M/Vt$$

Where, ρ_t - Tapped density (g/mL)

M - Mass of powder (g)

V_t - Tapped volume of the powder (mL).

8.5 Compressibility Index[61]

It indicates powder flow properties. It was measured for determining the relative importance of interparticulate interactions. It is expressed in percentage and is given by

$$CI = (\rho t - \rho b) / \rho t * 100$$

Where, CI – Compressibility Index

ρt - Tapped density,

ρb - Bulk density

8.6 Hausner's ratio[61]

Hausner's ratio is an index of ease of powder flow, it is calculated by following formula.

$$HR = \rho t \backslash \rho b$$

Where, HR - Hausner's ratio

ρt - Tapped density

ρb - Bulk density

Table No.7: Scale of Flowability [59]

Compressibility Index (%)	Flow Character	Hausner's Ratio
≤10	Excellent	1.00–1.11
11-15	Good	1.12-1.18
16-20	Fair	1.19-1.25
21-25	Passable	1.26-1.34
26-31	Poor	1.35-1.45
32-37	Very poor	1.46-1.59
>38	Very Very poor	>1.60

8.7 Angle of repose [61]

This is the maximum angle possible between the surface of the pile of powder and horizontal plane. The frictional forces in the loose powder can be measured by Angle of repose. The tangent of angle of repose is equal to the coefficient friction between the particles. Hence the rougher and more irregular surface of particles, the greater will be angle of repose.

Angle of repose was determined by using funnel method. Powder was poured from a funnel that can be raised vertically until a maximum cone height h, was obtained. Diameter of heap d was measured.

The angle of repose θ, was calculated by the formula,

$$\tan \theta = h/r$$

$$\theta = \tan^{-1}(h/r)$$

Where, θ - Angle of repose

h - Height of the pile (cm)

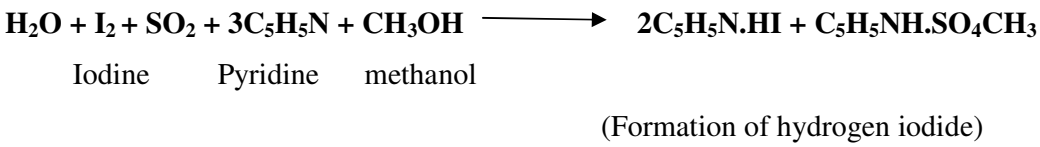
r - Radius of the pile (cm)

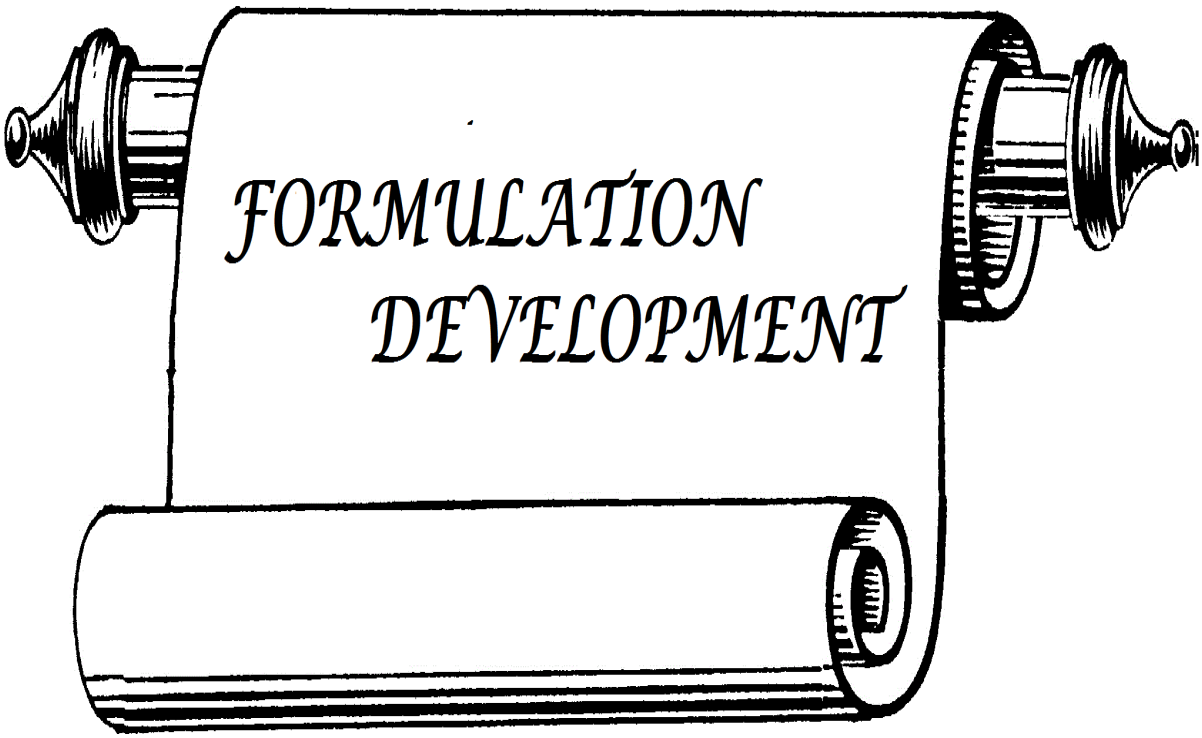
Table No. 8: Flow properties and corresponding Angles of Repose[60]

Flow property	Angle of Repose (Degrees)
Excellent	25-30
Good	31-35
Fair – aid not needed	36-40
Passable- may hang up	41-45
Poor –must agitate, vibrate	46-55
Very poor	56-65
Very Very poor	>66

8.8 Water Determination by Karl Fischer Titration[60]

Four tablets were powdered in a mortar and it was taken as analyte. The Karl Fischer reagent was added from automated burette and the endpoint was determined electrometrically. At the endpoint of the titration, a slight excess of the reagent increased the flow of current which was measured in milliamperes. The air in the system kept dry with a suitable dessicant and the titration vessel was purged by means of a stream of dry nitrogen or current of dry air.




FORMULATION
DEVELOPMENT

9. FORMULATION DEVELOPMENT

9.1 Excipient Selection

- Diluent - Pearlitol Flash (Mannitol with starch). Pearlitol flash is the widely used diluent in chewable and orally disintegrating tablets. It is a highly compressible and densified material which gives a compact tablet.[62]
- Sweetener – A combination of Saccharin Sodium and Aspartame was selected as sweetener.[49]
- Flavour – A combination of Mint and Orange flavour.[62]
- Disintegrant – Crospovidone (Polyplasdone XL 10) is one of the most widely used non ionic disintegrant which gives better disintegration at less concentration.[63]
- Wetting agent – In chewable tablet, ionic surfactants are avoided because they produce irritation on the mucosa. Hence Poloxamer 407 (Lutrol Micro 127) was selected which is a non ionic surfactant widely used in oral formulations.[64,65]
- Glidant – Colloidal Silicon Dioxide (Cabosil) was selected which is widely used to provide flow property and disintegration.[66]
- Lubricant – Sodium Stearyl Fumarate (Pruv) was selected since it is the only hydrophilic lubricant available in the market. It can be added in higher amounts in formulation without compromising on disintegration and dissolution characteristics of dosage form.[67]

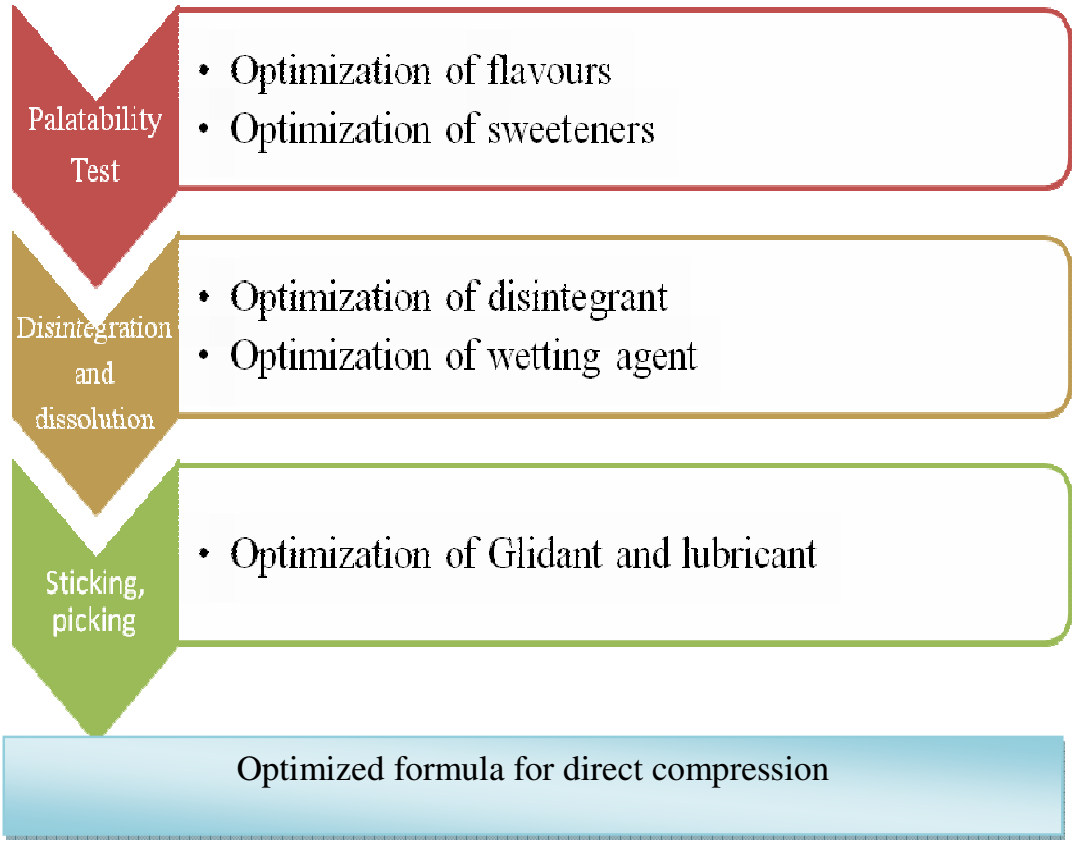
9.2 Punch Tooling

21 X 10 mm Caplet shaped punch.

9.3 Tablet Weight

Each tablet of 1200 mg weight.

FLOW CHART FOR OPTIMIZATION OF INGREDIENTS



9.4 Procedure

Step 1: Ubidecarenone, Pearlitol Flash, Crospovidone, Poloxamer 407, Mint Flavour, Orange Flavour, Aspartame and Saccharin Sodium were sifted through # 40 ASTM sieve.

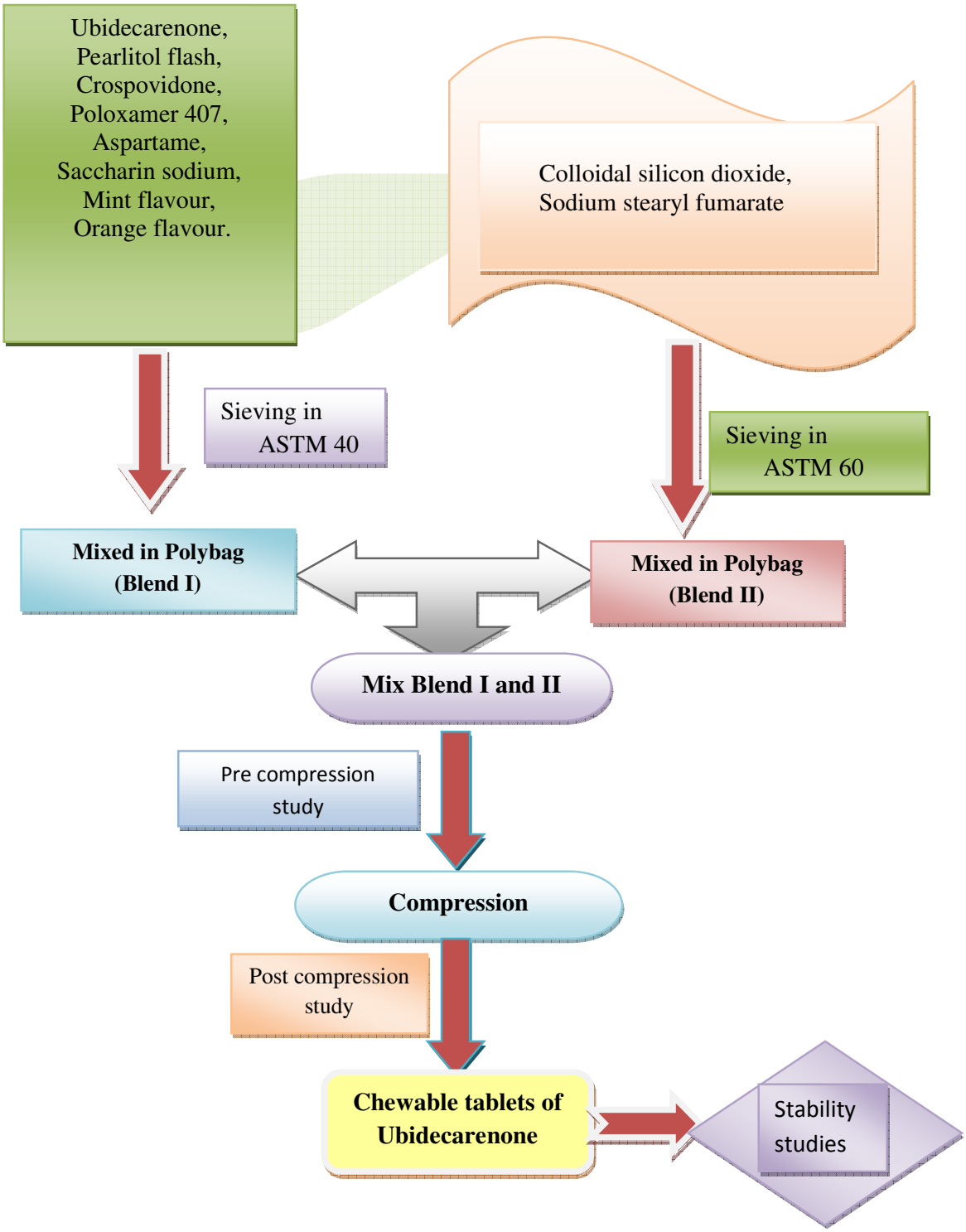
Step 2: The sifted materials of Step 1 was blended in a polybag for 10 min.

Step 3: Colloidal silicon dioxide and Sodium stearyl fumarate were sifted through # 60 ASTM sieve.

Step 4: The sifted materials of Step 3 and materials of Step 2 were mixed in a polybag for 5 min.

Step 5: The blended materials of Step 4 was compressed in 16 station tablet compression machine using 21 X 10 mm Caplet shaped punch.

FLOWCHART FOR MANUFACTURING PROCEDURE OF UBIDECARENONE CHEWABLE TABLETS



9.5 Formulation Trials for optimizing concentration of Flavours

The blends were prepared by varying the concentration of orange flavour, mint flavour and the concentration of all the other ingredients were kept constant. The tablets were compressed by direct compression technique in 16 station tablet compression machine using 21 x 10 mm caplet shaped punches.

Table No.9: Trials for optimizing concentration of Flavours

S.No	Ingredients	mg / tablet			
		A I	**A II**	**A III**	**A IV**
1	Ubidecarenone	400.00	400.00	400.00	400.00
2	Pearlitol Flash	757.50	757.50	757.50	757.50
3	Crospovidone	5.00	5.00	5.00	5.00
4	Poloxamer 407	5.00	5.00	5.00	5.00
5	Aspartame	5.00	5.00	5.00	5.00
6	Saccharin Sodium	5.00	5.00	5.00	5.00
7	**Mint Flavour**	**2.50**	**5.00**	**7.50**	**10.00**
8	**Orange Flavour**	**10.00**	**7.50**	**5.00**	**2.50**
9	Colloidal Silicon Dioxide	5.00	5.00	5.00	5.00
10	Sodium Stearyl Fumarate	5.00	5.00	5.00	5.00
Total		1200.00	1200.00	1200.00	1200.00

The formulated tablets were evaluated and concentration of flavours were optimized based on aroma sensation testing by volunteers.

9.6 Formulation trials for optimizing concentration of Sweeteners

The blends were prepared by varying the concentration of aspartame, saccharin sodium and the concentration of all the other ingredients were kept constant. The tablets were compressed by direct compression technique in 16 station tablet compression machine using 21 x 10 mm caplet shaped punches.

Table No.10: Trials for optimizing concentration of Sweeteners

S.No	Ingredients	mg / tablet			
		B I	**B II**	**B III**	**B IV**
1	Ubidecarenone	400	400	400	400
2	Pearlitol Flash	742.5	742.5	742.5	742.5
3	Crospovidone	5.00	5.00	5.00	5.00
4	Poloxamer 407	5.00	5.00	5.00	5.00
5	**Aspartame**	**5.00**	**10.00**	**15.00**	**20.00**
6	**Saccharin Sodium**	**20.00**	**15.00**	**10.00**	**5.00**
7	Mint Flavour	10.00	10.00	10.00	10.00
8	Orange Flavour	2.5	2.5	2.5	2.5
9	Colloidal Silicon Dioxide	5.00	5.00	5.00	5.00
10	Sodium Stearyl Fumarate	5.00	5.00	5.00	5.00
Total		1200.00	1200.00	1200.00	1200.00

The formulated tablets were evaluated and Concentration of Sweeteners were optimized based on taste evaluation by volunteers.

9.7 Formulation trials for optimizing concentration of Disintegrant

The blends were prepared by varying the concentration of Crospovidone (Polyplasdone XL10) and the concentration of all the other ingredients were kept constant. The tablets were compressed by direct compression technique in 16 station tablet compression machine using 21 x 10 mm caplet shaped punches.

Table No.11: Trials for optimizing concentration of Disintegrant

S.No	Ingredients	mg / tablet			
		C I	**C II**	**C III**	**C IV**
1	Ubidecarenone	400.00	400.00	400.00	400.00
2	Pearlitol Flash	727.5	707.5	687.5	667.5
3	**Crospovidone**	**20.00**	**40.00**	**60.00**	**80.00**
4	Poloxamer 407	5.00	5.00	5.00	5.00
5	Aspartame	20.00	20.00	20.00	20.00
6	Saccharin Sodium	5.00	5.00	5.00	5.00
7	Mint Flavour	10.00	10.00	10.00	10.00
8	Orange Flavour	2.50	2.50	2.50	2.50
9	Colloidal Silicon Dioxide	5.00	5.00	5.00	5.00
10	Sodium Stearyl Fumarate	5.00	5.00	5.00	5.00
Total		1200.00	1200.00	1200.00	1200.00

The formulated tablets were evaluated and concentration of Crospovidone was optimized based on the disintegration time of tablets.

9.8 Formulation trials for optimizing concentration of Wetting Agent

The blends were prepared by varying the concentration of Poloxamer 407 (wetting agent) and the concentration of all the other ingredients were kept constant. The tablets were compressed by direct compression technique in 16 station tablet compression machine using 21 x 10 mm caplet shaped punches.

Table No.12: Trials for optimizing of Concentration of Wetting Agent

S.No	Ingredients	mg / tablet			
		D I	**D II**	**D III**	**D IV**
1	Ubidecarenone	400.00	400.00	400.00	400.00
2	Pearlitol Flash	692.5	687.5	682.5	677.5
3	Crospovidone	60.00	60.00	60.00	60.00
4	**Poloxamer 407**	**-**	**5.00**	**10.00**	**15.00**
5	Aspartame	20.00	20.00	20.00	20.00
6	Saccharin Sodium	5.00	5.00	5.00	5.00
7	Mint Flavour	10.00	10.00	10.00	10.00
8	Orange Flavour	2.50	2.50	2.50	2.50
9	Colloidal Silicon Dioxide	5.00	5.00	5.00	5.00
10	Sodium Stearyl Fumarate	5.00	5.00	5.00	5.00
Total		1200.00	1200.00	1200.00	1200.00

The formulated tablets were evaluated and concentration of poloxamer 407 was optimized based on their dissolution profile of tablets.

9.9 Formulation trials for optimizing concentration of Glidant & Lubricant

The blends were prepared by varying the concentration of glidant (colloidal silicon dioxide), lubricant (Sodium stearyl fumarate) and the concentration of all the other ingredients were kept constant. The tablets were compressed by direct compression technique in 16 station tablet compression machine using 21 x 10 mm caplet shaped punches.

Table No.13: Trials for optimizing of Concentration of Glidant & Lubricant

S.No	Ingredients	mg / tablet			
		E I	**E II**	**E III**	**E IV**
1	Ubidecarenone	400.00	400.00	400.00	400.00
2	Pearlitol Flash	644.5	656.5	680.5	668.5
3	Crospovidone	60.00	60.00	60.00	60.00
4	Poloxamer 407	10.00	10.00	10.00	10.00
5	Aspartame	20.00	20.00	20.00	20.00
6	Saccharin Sodium	5.00	5.00	5.00	5.00
7	Mint Flavour	10.00	10.00	10.00	10.00
8	Orange Flavour	2.50	2.50	2.50	2.50
9	**Colloidal Silicon Dioxide**	**24.00**	**18.00**	**6.00**	**12.00**
10	**Sodium Stearyl Fumarate**	**24.00**	**18.00**	**6.00**	**12.00**
Total		1200.00	1200.00	1200.00	1200.00

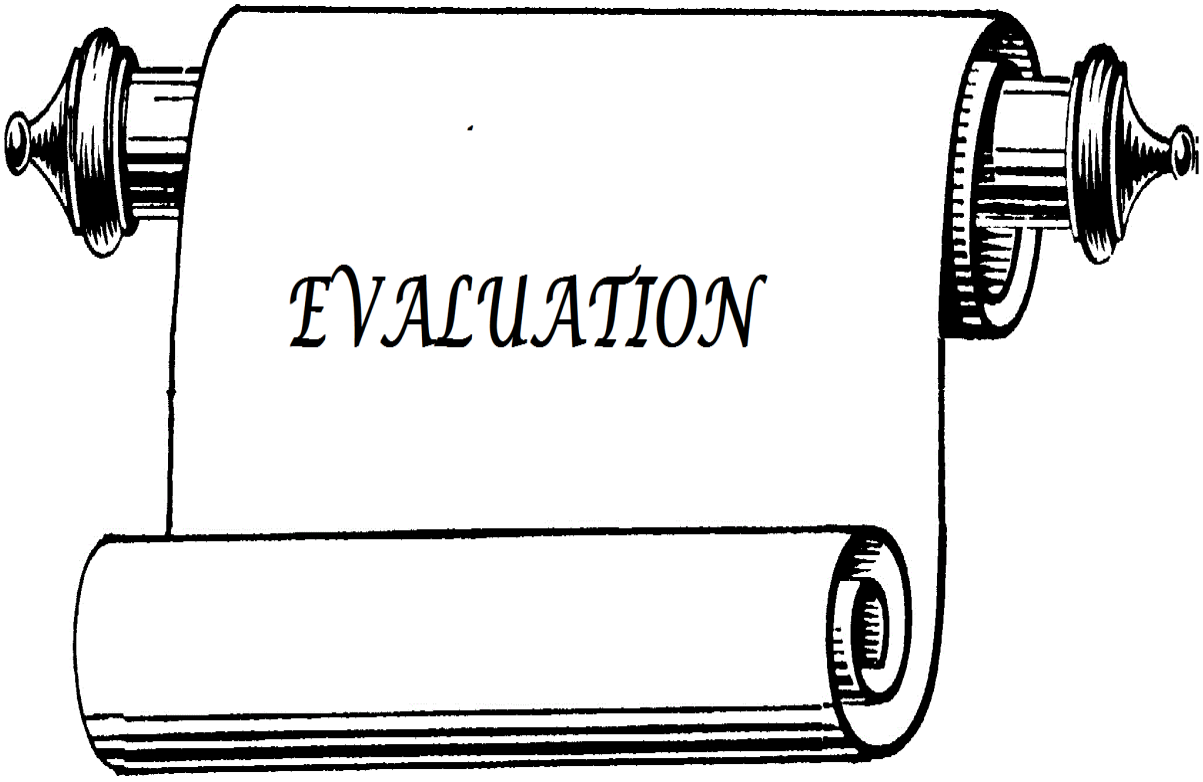
The formulated tablets were evaluated for its physical characteristics such as sticking, picking, striation and the concentration of glidant (Cabosil) and lubricant (Sodium stearyl fumarate) was optimized.

Formulation of Optimized batch

Table No.14: Formula for Optimized Batch (E III)

S.No	Ingredients	mg / tablet
1	Ubidecarenone	400.00
2	Pearlitol Flash	680.5
3	Crospovidone	60.00
4	Poloxamer 407	10.00
5	Aspartame	20.00
6	Saccharin Sodium	5.00
7	Mint Flavour	10.00
8	Orange Flavour	2.50
9	Colloidal Silicon Dioxide	6.00
10	Sodium Stearyl Fumarate	6.00
Total		1200.00

The optimized formulation blend was mixed uniformly and it was compressed by direct compression technique in 16 station tablet compression machine using 21 x 10 mm caplet shaped punches.


EVALUATION

10. EVALUATION OF CHEWABLE TABLETS

10.1 Appearance

The general appearance of the tablet was studied by the evaluation of the parameters like size, colour and odour.

Procedure: 10 tablets were visually observed.

10.2 Thickness[68]

The thickness of the tablet was measured to determine the uniformity of size and shape.

Procedure: The thickness of the tablet was measured using Vernier caliper.

10.3 Friability[69]

Friability of the prepared formulations was determined by using Roche friabilator. Pre weighed sample of tablets was placed in the friability tester, which was then operated for 100 revolutions, tablets were dedusted and reweighed. The friability of the tablets was calculated using the formula mentioned below,

$$\% \text{ Friability} = \frac{\text{Initial weight} - \text{Final weight}}{\text{Initial weight}} \times 100$$

A friabilator evaluates the ability to withstand mechanical stress during packaging, handling and shipping.

10.4 Hardness[70]

The hardness test was performed to measure the tablet strength. Tablets should be hard enough to withstand packaging and shipping but not so hard as to create difficulty upon chewing.

- **Procedure:** Tablets were taken and its hardness were tested by using Dr. Schleuniger Pharmatron model 5Y tablet tester and the readings were noted.

10.5 Uniformity of weight[71]

20 tablets were selected randomly and weighed individually and the average weight was calculated. Then the individual weight was compared to the average weight. Not more than two of the individual weights deviate from the average weight by the percentage deviation given below.

Table No. 15: Average weight and its % deviation allowed

S.No	Average weight of the tablet(mg)	Percentage deviation allowed
1	130 or less	10.0%
2	More than 130 but less than 324	7.5%
3	More than 324	5.0%

10.6 Palatability Test[72, 73]

Organoleptic evaluation for the formulated tablets were carried out by the study of palatability of tablets. The sweetness, bitterness, mouth feel, aftertaste and flavour evaluated as a parameter for the tablets. For this test, 5 healthy volunteers were selected and they were asked to chew the tablets in the mouth. Immediately after the evaluation, the volunteers were asked to rinse their mouth the volunteers without ingesting the disintegrated particles.

10.7 Disintegration[74, 75]

This test is provided to determine whether tablets disintegrate within the prescribed time when placed in a liquid medium at the experimental conditions. Complete disintegration is defined as that state in which any residue of the unit except fragments of insoluble coating or capsule shell, remaining on the screen of the test apparatus or adhering to the lower surface of the disc, if used is a soft mass having no palpably firm core.

- **UNCOATED TABLETS**

One dosage unit in each of the six tubes of the basket were placed. The apparatus was operated using water as the immersion fluid, maintained at 37º ±2ºC. The time taken for complete disintegration of tablets was noted.

10.8 ASSAY[60,76]

- **Instrumentation**

A liquid chromatograph consists of a fixed volume injector loop with a UV-Visible Spectrophotometer detector and data management software.

- **Chemicals and Reagents**

  - Solvent - a mixture of n-hexane and dehydrated alcohol (5:2).
  - Mobile phase - a filtered and degassed mixture of Acetonitrile, Tetrahydrofuran and Water (55:40:5).
  - Water (HPLC grade)
  - **Standard preparation** - An accurately weighed quantity of USP Ubidecarenone RS in the above solvent was taken to get a solution having a known concentration of 1.0 mg per mL was prepared. Then a portion of this solution was diluted with dehydrated alcohol to obtain a solution having a known concentration of about 40 µg per mL.
  - **Resolution solution** - An accurately weighed quantity of USP Ubidecarenone Related Compound A RS in the above solvent was taken to get a solution having a concentration of 1.0 mg per mL. Then a portion of this solution was diluted with dehydrated alcohol to obtain a solution having a concentration of about 40 µg per mL. Mix equal volumes of this solution and the Standard preparation.
  - **Test preparation (Assay)**

    20 Tablets were weighed and powdered. An accurately weighed quantity of the powder equivalent to about 100 mg of Ubidecarenone was transferred to a 100 mL volumetric flask, add 6 mL of Solvent[mixture of n-hexane and dehydrated alcohol (5:2)] and shaken by mechanical means for 30 minutes. It was diluted with the solvent mixture upto the volume and mixed. It was centrifuged and 1 mL of the supernatant was transferred to a 25 mL volumetric flask, 2.5 mL of a 0.1% solution of anhydrous ferric chloride in alcohol was added, diluted with alcohol to volume and mixed.

➢ **Procedure**

Equal volume (about 15 µL) of the Standard preparation and the Assay preparation was injected separately in L1 column. The chromatograms were recorded and the responses were measured for the major peaks.

The quantity of Ubidecarenone ($C_{59}H_{90}O_4$) was calculated by the formula:

$$2500C(r_U / r_S)$$

Where, C- Concentration, in mg per mL of USP Ubidecarenone RS in the Standard preparation,

r_U and r_S - Peak responses obtained from the Assay preparation and the Standard preparation, respectively.

➢ **The System Suitability Parameters**

- The resolution R, between Ubidecarenone and Ubidecarenone related compound A - NLT 2.5.
- The tailing factor - NMT 1.5
- Relative standard deviation for replicate injections - NMT 2.0%.

10.9 BUFFER PREPARATION DETAILS[60]

➢ **Preparation of pH 6.8 Phosphate buffer solution**

Place 50mL of the monobasic potassium phosphate solution in a 200mL volumetric flask and add 22.4mL of 0.2M sodium hydroxide solution then add water to make up the volume.

➢ **Preparation of 0.2M Sodium Hydroxide**

Dissolve 8g of sodium hydroxide in 1000mL of distilled water.

➢ **Preparation of 1% Sodium lauryl sulphate**

Dissolve 1g of sodium lauryl sulphate in 100mL of distilled water.

10.10 DISSOLUTION APPARATUS SPECIFICATIONS[77]

Apparatus	: Type I (USP)
Medium	: Phosphate buffer pH 6.8
Volume	: 900ml
Speed	: 100rpm
Temperature	: 37º C ± 0.5º C
Time points	: 10, 20, 30, 40, 50, 60, 75, 90 and 120 minutes.

The amount of Ubidecarenone released was determined by chromatographic technique.

- **Chromatographic specifications[60]**

Buffer solution	: Phosphate buffer pH 6.8
Mobile Phase	: Mixture of Methanol and dehydrated alcohol
Column	: 5mm x 15cm column that contains packing L1
Column temperature	: 35ºC
Injection	: 5µl
Detection	: Spectrophotometer at 275 nm

- **Procedure**

Equal volumes (about 5 µL) of the Standard preparation and the Assay preparation were injected separately into the chromatograph, the chromatograms were recorded and responses were measured for the major peaks. The quantity of Ubidecarenone in mg was calculated.

$$\mathbf{50C\ (r_U / r_S)}$$

Where,

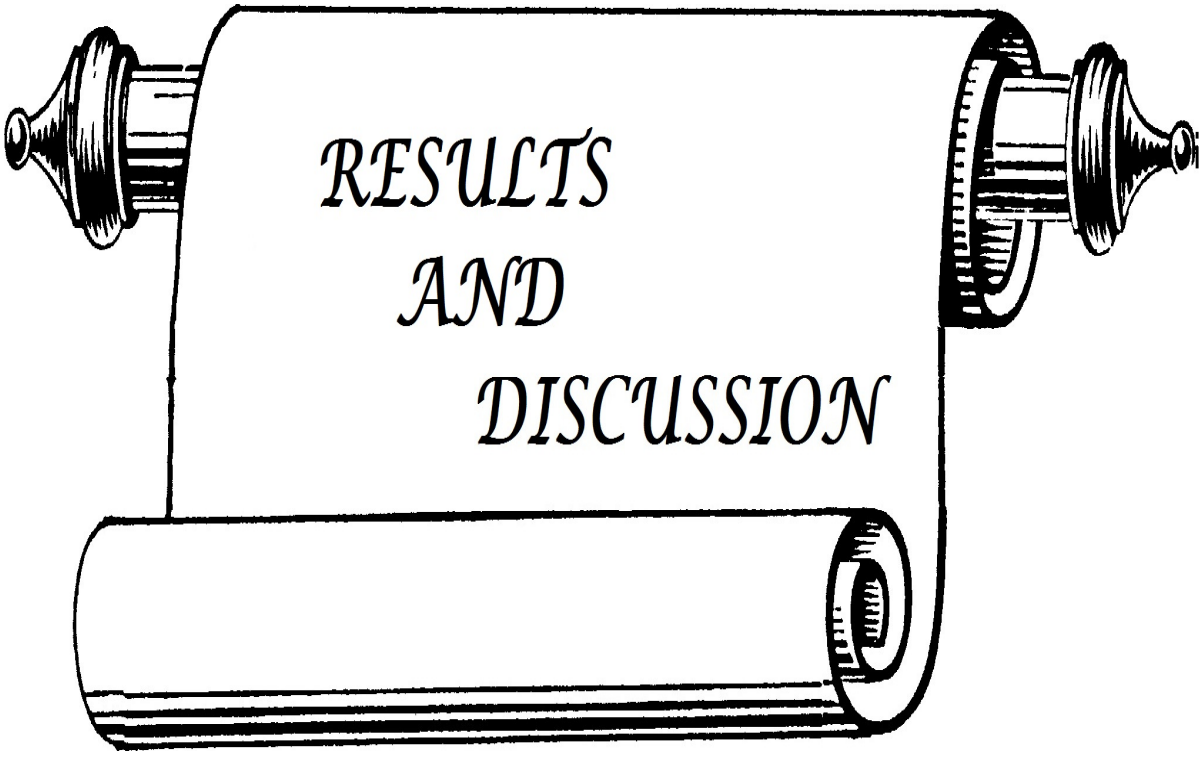
C- Concentration in mg per mL of USP Ubidecarenone RS in the Standard preparation.

r_U and r_S - peak responses obtained from the Assay preparation and the Standard preparation respectively.

10.11 STABILITY STUDY[78]

Tablets were packed in 75 cc Amber Coloured HDPE Bottle with 33 mm PP Child Resistant Closure. It was done to generate information regarding the shelf life of the formulation and its recommended storage conditions.

Accelerated stability test was carried out by keeping the final pack under the condition 40±2ºC/75±5%RH and the various parameters such as description, disintegration, assay, dissolution and water content were evaluated for the samples withdrawn at the time interval of 1st month, 2nd month and 3rd month.


RESULTS
AND
DISCUSSION

11. RESULTS AND DISCUSSION

11.1 DRUG- EXCIPIENT COMPATIBILITY STUDY

Table No. 15: Ubidecarenone – Excipient Compatibility (Initial)

S. No	Drug-Excipient	Ratio	Initial		Appearance
			Assay (%)	Water Content(%)	
1	UB – Pearlitol Flash	1:0.5	98.0	3.38	Yellowish white powder
2	UB – Crospovidone	1:0.25	97.0	3.95	White to off white powder
3	UB – Poloxamer 407	1:0.25	99.0	1.97	Orange yellowish powder
4	UB – Aspartame	1:0.25	97.0	4.12	Orange yellowish powder
5	UB–Saccharin Sodium	1:0.25	96.0	4.98	Orange yellowish powder
6	UB – Mint Flavour	1:0.25	98.0	3.67	Orange yellowish powder
7	UB – Orange Flavour	1:0.25	99.0	3.83	Orange yellowish powder
8	UB–Colloidal Silicon Dioxide	1:0.25	98.0	3.72	Yellow whitish powder
9	UB–Sodium Stearyl Fumarate	1:0.25	97.0	2.12	Orange yellowish powder

Table No. 16: Ubidecarenone – Excipient Compatibility (Accelerated Stability Study)

S. No	Drug-Excipient	Ratio	40°C/ 75%RH-2nd week		Appearance	40°C/ 75%RH-4th Week		Appearance
			Assay (%)	Water Content (%)		Assay (%)	Water content (%)	
1	UB – Pearlitol Flash	1:0.5	96.12	3.28	NC	96.87	3.23	NC
2	UB – Crospovidone	1:0.25	95.84	3.81	NC	95.62	3.61	NC
3	UB – Poloxamer 407	1:0.25	97.65	1.90	NC	97.54	1.75	NC
4	UB – Aspartame	1:0.25	95.84	4.06	NC	95.61	4.46	NC
5	UB – Saccharin Sodium	1:0.25	94.64	4.89	NC	94.91	4.43	NC
6	UB – Mint Flavour	1:0.25	97.58	3.59	NC	97.64	3.72	NC
7	UB – Orange Flavour	1:0.25	96.72	3.78	NC	96.98	3.84	NC
8	UB – Colloidal Silicon Dioxide	1:0.25	95.64	3.67	NC	95.35	3.24	NC
9	UB – Sodium Stearyl Fumarate	1:0.25	95.67	1.99	NC	95.64	1.62	NC

UB- Ubidecarenone, NC - No change.

Inference

From the above results

- It was found the drug content was within the limits.
- No change in physical appearance.

Thus it was found that all the excipients were compatible with drug.

11.2 API CHARACTERIZATION

Ubidecarenone raw material was analyzed for the parameters like particle size distribution, derived properties like bulk density, tapped density, Compressibility Index, Hausner's ratio and Angle of Repose.

➢ Particle size distribution of Ubidecarenone

Table No. 17: Particle size distribution of Ubidecarenone

S.No	ASTM Sieve No.	Empty Sieve weight (g)	Weight of Sieve + sample retained (g)	Weight of sample retained (g)	% Sample retained	Cumulative % retained
1	20	364	366.5	2.5	12.5	12.5
2	40	363	367.5	4.5	22.5	35.0
3	60	341.5	345	3.5	17.5	52.5
4	80	336	337.5	1.5	7.5	60.0
5	100	331.5	333	1.5	7.5	67.5
6	140	333	334.5	1.5	7.5	75.0
7	200	307	310.5	3.5	17.5	92.5
8	Pan	498.5	500	1.5	7.5	100

From the above table it is clear that maximum particles were retained on sieve No. 40.

➢ Derived properties of Ubidecarenone

Table No. 18: Derived properties of Drug

Bulk density (g/mL)	0.446
Tapped density (g/mL)	0.657
Compressibility index (%)	32.14
Hausner's Ratio	1.47
Angle of Repose (θ)	37 º 48'

The Ubidecarenone raw material had very poor flow property. Therefore the drug was blended with the excipients to improve the flow property.

11.3 Formulation Trials for optimizing concentration of Flavours

In these trials, concentration of mint flavour and orange flavour were varied, keeping concentration of all the other ingredients as constant and Four trials (AI, AII, AIII, A IV) were formulated and the concentration of flavouring agents was optimized based on evaluation by volunteers.

Table No. 19: Flavour Assessment [72]

Flavour score	Report
0-2	Poor
3	Average
4	Acceptable
5	Good

Table No. 20: Evaluation of Flavour by Volunteers

	Flavour score			
Volunteer	**A I**	**A II**	**A III**	**A IV**
I	2	3	4	5
II	1	3	4	5
III	1	3	4	5
IV	1	3	4	5
V	1	3	4	5

Flavour was evaluated by human healthy volunteers. Five volunteers were involved in evaluating the flavour and the score for flavour is given in the range of 0-5.

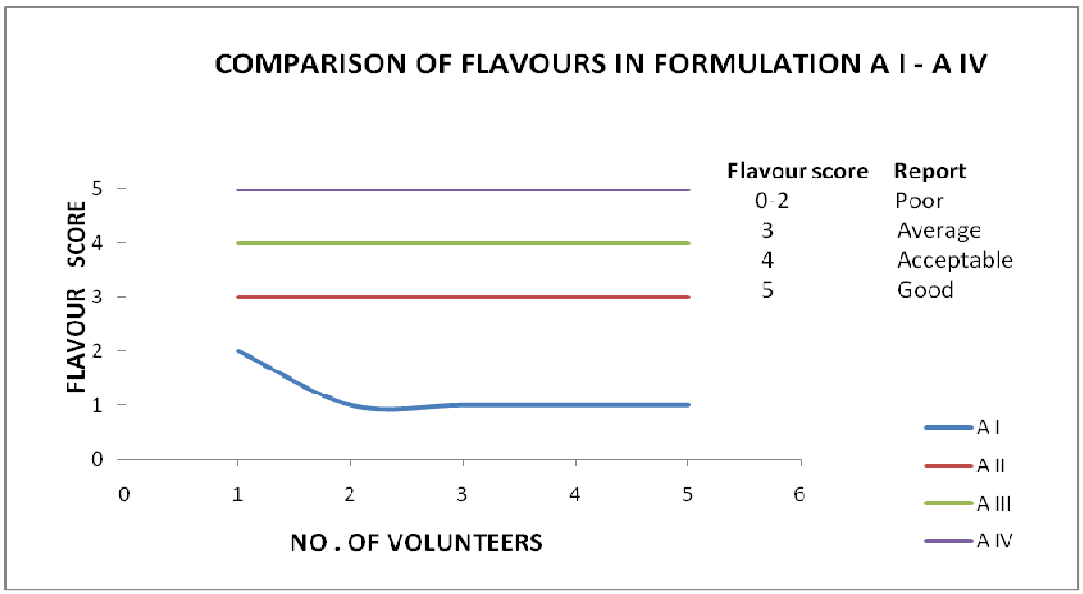


Fig 4: Comparison of Flavours in Formulation A I – A IV

Inference

Formulation A IV was selected as it had good flavour by the reports from the volunteers and thus concentration of Orange flavour (0.21%) and Mint flavour (0.83%) were optimized.

11.4 Formulation Trials for optimizing concentration of Sweeteners

In these trials, concentration of sweetening agents were varied, keeping concentration of all the other ingredients constant and Four trials (B I, B II, B III, B IV) were formulated and the concentration of sweetening agents was optimized based on evaluation by volunteers.

Table No. 21: Taste Assessment [72]

Sweet score	Report
0-2	Poor
3	Average
4	Acceptable
5	Good

Table no. 22: Evaluation of Taste by Volunteers

	Sweet score			
Volunteer	**B I**	**B II**	**B III**	**B IV**
I	1	3	4	5
II	1	3	4	5
III	1	3	4	5
IV	1	3	4	5
V	2	3	4	5

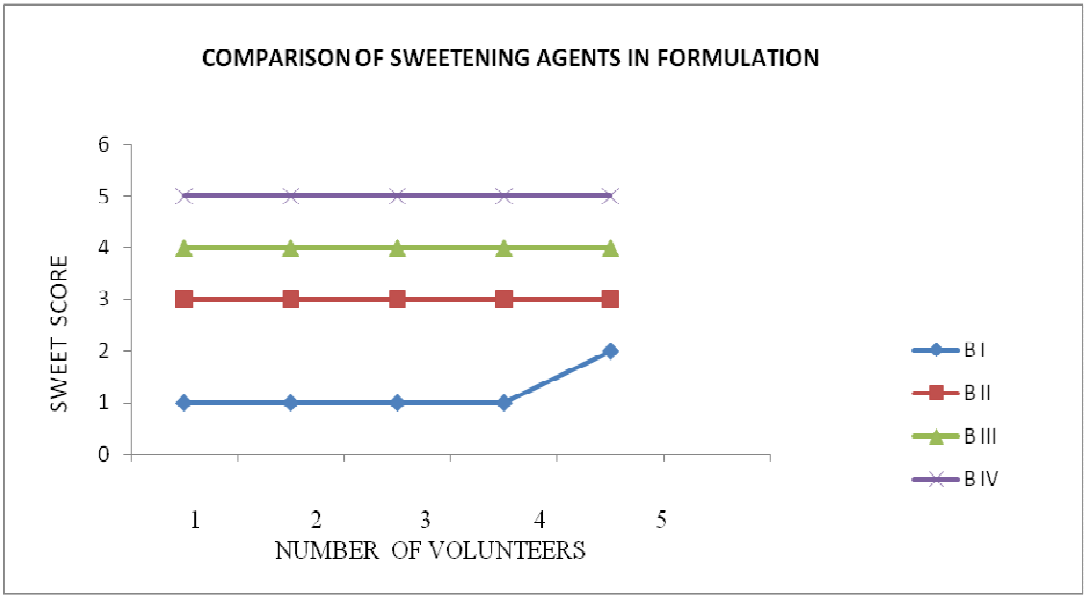


Fig 5: Comparison of Sweetening Agents in Formulation B I - BIV

Inference

Formulation B IV was selected, as it had Good taste by the reports from the volunteers and thus the concentration of sweetening agents Aspartame (1.6%) and Sodium Saccharin (0.4%) were optimized.

11.5 Formulation Trials for optimizing concentration of Disintegrant

In these trials, concentration of Crospovidone was varied, keeping concentration of all the other ingredients as constant and Four trials (C I, C II, C III, C IV) were formulated and the concentration of disintegrating agent was optimized based on disintegration time of tablets.

Table No. 23: Comparison of Disintegration time for formulations (C I – C IV)

Disintegration time (min)*			
C I	C II	C III	C IV
9’ 47” ±0.8695	5’ 10” ±0.6082	1’ 22” ±0.1408	1’ 47” ±0.3209

*** Mean ± SD (n=6)**

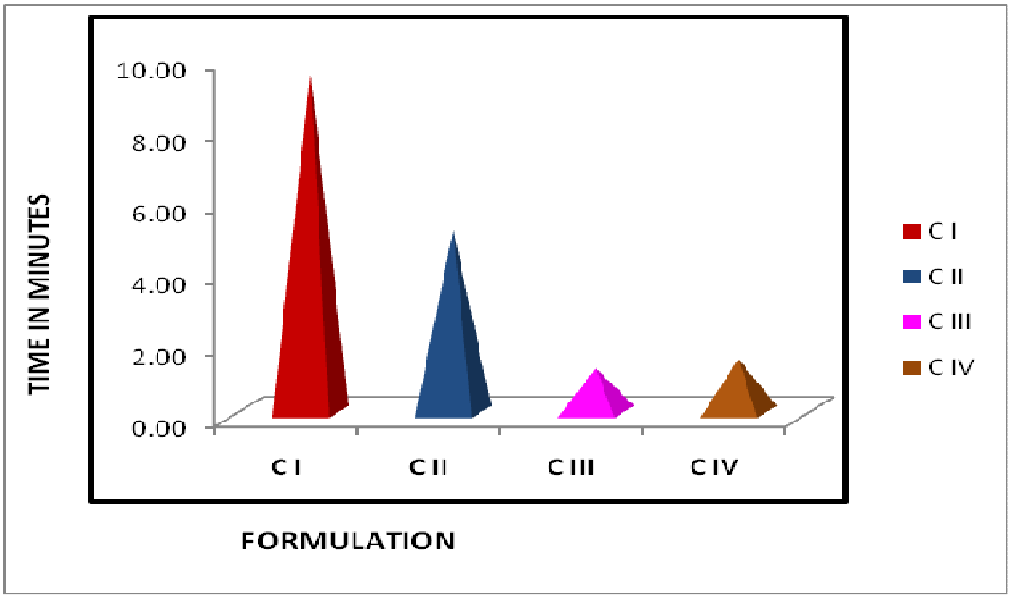


Fig 6: Comparison of disintegration time for formulations C I – C IV

Inference

The Formulation C III was found to have faster disintegration compared to other three formulations. Thus the formulation C III containing 5% of Crospovidone was optimized.

11.6 Formulation Trials for optimizing concentration of Wetting Agent

In these trials, concentration of Poloxamer 407 was varied, keeping concentration of all the other ingredients as constant and Four trials (D I, D II, D III, D IV) were formulated and the concentration of wetting agent was optimized based on dissolution profile of tablets.

Table No. 24: *In vitro* drug release for the batches D I – D IV

Time (Min)	Cumulative % Drug Release *			
	D I	**D II**	**D III**	**D IV**
10	18.66 ±0.6437	24.76 ±0.5936	30.81 ±0.2693	37.33 ±0.5368
20	29.72 ±0.5118	41.47 ±0.6810	55.13 ±0.7435	58.72 ±0.5204
30	33.75 ±0.4235	61.21 ±0.5449	75.38 ±0.5602	77.74 ±0.7184
45	**42.35 ±0.2286**	**71.39 ±0.5610**	**85.41 ±0.4077**	**88.25 ±0.1662**
60	54.88 ±0.4194	82.45 ±0.5246	95.33 ±0.3454	98.91 ±0.3802
75	61.43 ±0.7650	90.78 ±0.7457	97.59 ±0.8941	99.60 ±0.0854
90	80.88 ±0.6077	98.32 ±0.2938	99.40 ±0.1845	99.80 ±0.0681
120	89.17 ±0.4712	98.66 ±0.2307	99.60 ±0.2168	98.43 ±0.0854

*** Mean ± S.D (n = 6)**

USP limits: Q value not less than 75% at the end of 45 minutes [2]

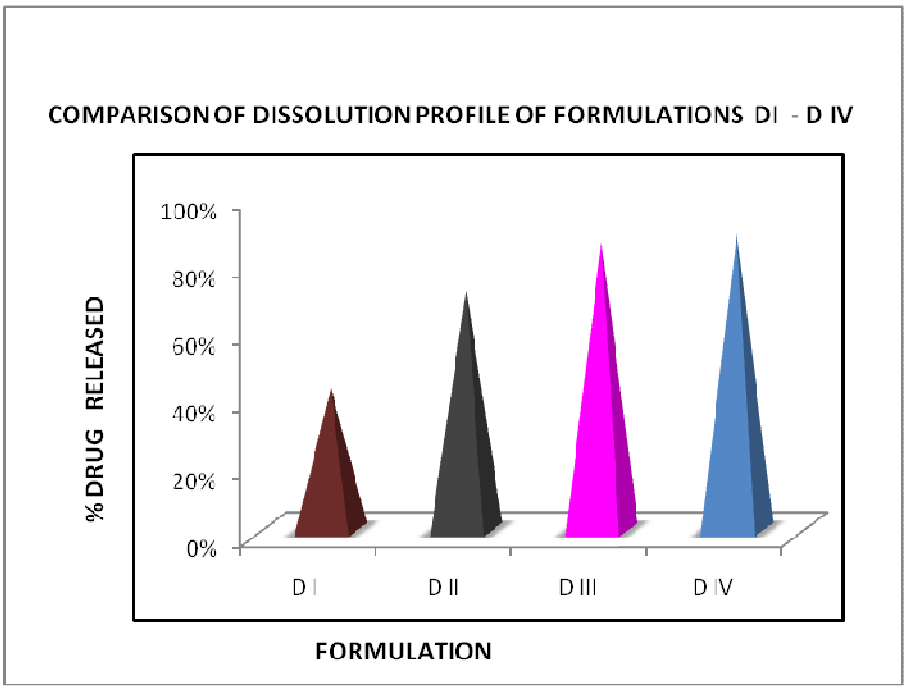


Fig 7: Comparison of dissolution profile for Formulations D I – D IV

➢ Inference

Formulations D III and D IV having Poloxamer 407 concentration (0.83%) and (1.25%) resulted in 85.41% and 88% of drug release respectively at the end of 45 minutes. The formulation D III had desired release (Q value not less than 75%). Thus formulation D III having 0.83% of Poloxamer 407 was optimized.

11.7 Formulation Trials for optimizing concentration of Glidant & Lubricant

In these trials, concentration of Colloidal silicon dioxide (Glidant) and Sodium stearyl fumarate (Lubricant) were varied, keeping concentration of all the other ingredients as constant and Four trials (E I, E II, E III, E IV) were formulated and various physical characteristics such as sticking, picking and striation were investigated.

Table No. 25: Post Compression Evaluation of Defects in Tablets for Formulations (EI – EIV)

S.No	Parameter	E I	E II	E III	E IV
1	Picking	×	×	×	×
2	Sticking	×	×	×	×
3	Striation	×	×	×	×
4	Remarks	No defect	No defect	No defect	No defect

✓ - Present × - Absent

Inference

All the Formulations E I to E IV were found to be free from sticking, picking and striation. The Formulation E III having low concentration of Colloidal silicon dioxide (0.5%) and Sodium stearyl fumarate (0.5%) was optimized.

11.8 FINALIZED FORMULATION (E III) AND ITS CHARACTERIZATION

Table No. 26: Ingredients of the Optimized Batch (E III)

S.No	Ingredients	mg / tablet
1	Ubidecarenone	400.00
2	Pearlitol Flash	680.50
3	Crospovidone	60.00
4	Poloxamer 407	10.00
5	Aspartame	20.00
6	Saccharin Sodium	5.00
7	Mint Flavour	2.50
8	Orange Flavour	10.00
9	Colloidal silicon dioxide	6.00
10	Sodium stearyl fumarate	6.00
Total		**1200.00**

Table No. 27: Pre Compression Parameters of Optimized Batch (E III)

S.No	Parameter	E III batch
1	Bulk Density (g/mL)*	0.4732 ± 0.0157
2	Tapped Density (g/mL)*	0.6121 ± 0.0017
3	Compressibility Index (%)*	22.70 ± 2.719
4	Hausner's Ratio *	1.30 ± 0.0462
5	Angle of Repose (θ)	32.20

*** Mean ±SD (n=3)**

- The flow property of blend is graded as "good" based on Angle of repose value.

Table No. 28: Post compression parameters of Optimized Batch (E III)

Parameter	E III batch
Uniformity of weight (g)***	1.204 ±0.0021
Thickness (mm)*	4.57 ±0.0440
Hardness (kp)*	11.0 ±0.3162
Friability (%)	0.394
Disintegration Time (min)**	1' 46" ±0.0732
Assay (%)	98.14

*** Mean ±SD (n=5), **Mean ±SD (n=6), ***Mean ±SD (n=20)**

The formulated tablets were found to be

- Uniform in weight.
- Uniform in thickness.
- Friability was within the limits.
- Disintegration time was within the limits.
- Drug content by assay complies with USP limits.

Table No. 29: Palatability test for Optimized Formulation (E III)

Volunteer	Sweet score	Flavour score
	E III	E III
I	5	5
II	5	5
III	5	5
IV	5	5
V	5	4
Report	Good	Good

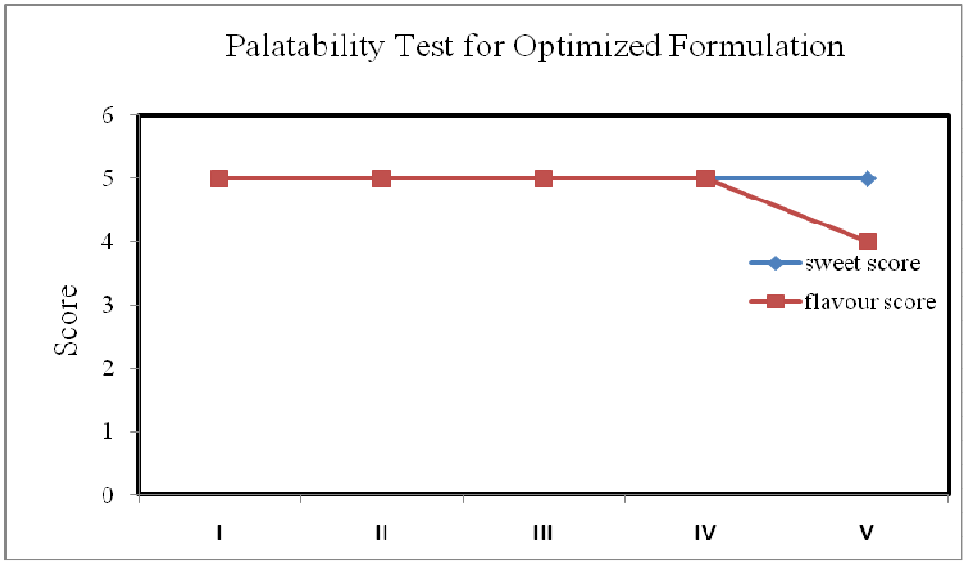


Fig 8: Palatability test for Optimized batch (E III)

The sweet and flavour for the optimized batch was found to be good based on reports by the volunteers.

Table No. 30: *In vitro* release study for the Optimized batch (E III)

Parameter	**E III batch**
Dissolution	USP-I (Basket), 100 rpm, 900 ml, pH 6.8 Phosphate buffer + 1% SLS.
Time (min)	**Cumulative % Drug Release***
10	37.19 ± 0.3894
20	58.88 ± 0.1930
30	77.54 ± 0.9681
45	**88.65 ± 0.3530**
60	98.85 ± 0.4619
75	99.40 ±0.1401
90	99.52 ±0.2309
120	98.51 ± 0.0513

*** Mean ±SD (n=6)**

The *in vitro* drug release of the optimized batch was found to be 88.65% at the end of 45 minutes and 99.52% at the end of 90 minutes.

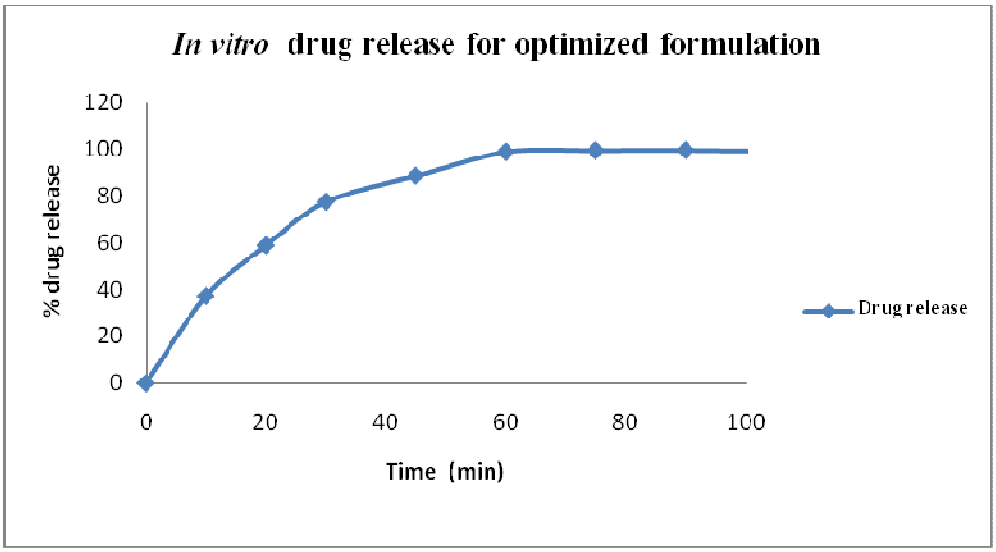


Fig 9: *In vitro* drug release for Optimized formulation (E III)

11.9 STABILITY STUDIES

- **Pack**

75cc Amber Coloured HDPE Bottle with 33 mm PP Child Resistant Closure with Induction Seal Liner With 1 g per bottle of 6 g/yard Cotton as dunnage and 2 numbers of 1 g Silica gel canister as desiccant.

Count: 30 Tablets / bottle

Table No. 31: Stability study of Optimized Formulation (E III)

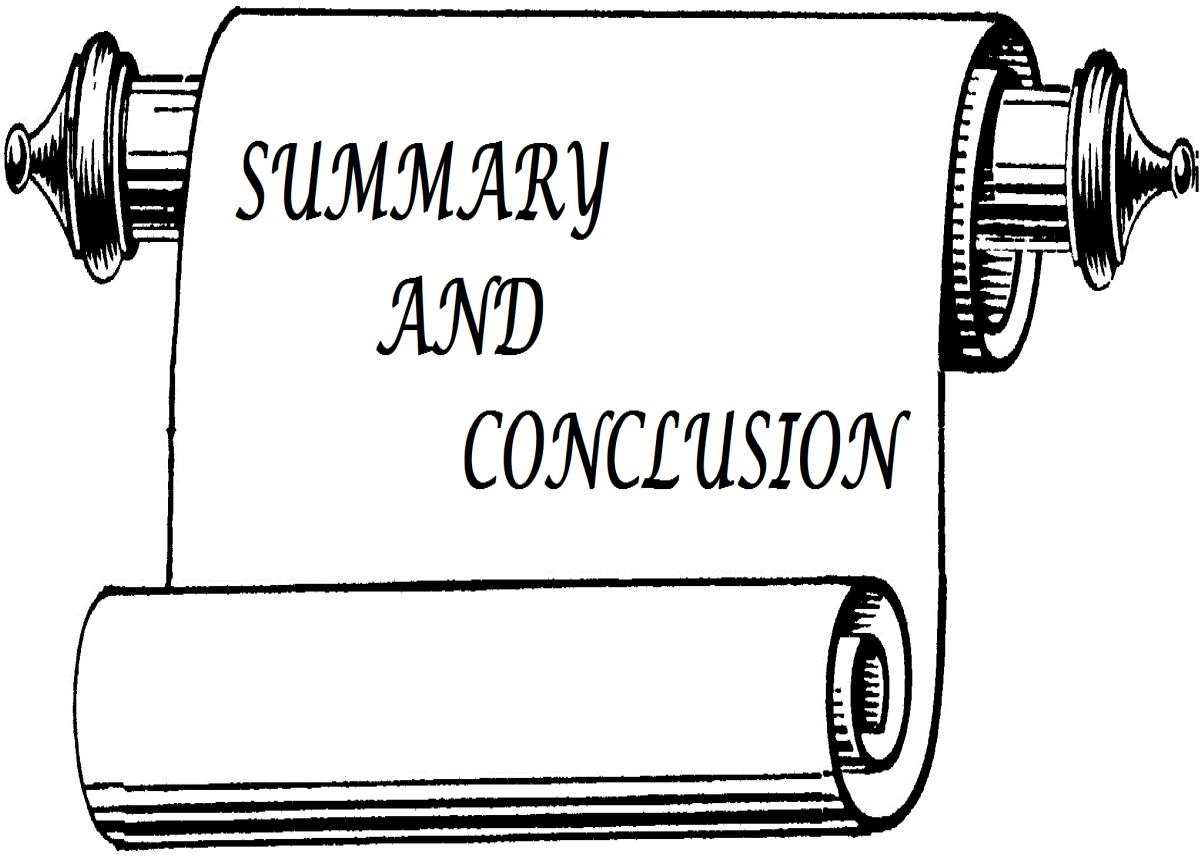
S. No	Parameters	Initial	1st month	2nd month	3rd month
1	Description	White to off-white shaped tablets	White to off-white shaped tablets	White to off-white shaped tablets	White to off-white shaped tablets
2	Uniformity of weight(g) *	1.204 ± 0.0021	1.203 ± 0.0021	1.203 ± 0.0025	1.202 ± 0.0027
3	Thickness(mm)**	4.57 ± 0.0440	4.57 ± 0.0150	4.56 ± 0.0172	4.55 ± 0.0160
4	Hardness(Kp)**	11.0 ± 0.3162	11.12 ± 0.2315	11.08 ± 0.1939	11.08 ± 0.2400
5	Friability (%)	0.367	0.393	0.390	0.403
6	Disintegration time (min) ***	1’ 52” ± 0.0732	1’ 47” ± 0.0654	1’ 43” ± 0.0528	1’ 45” ± 0.0802
7	Water content by KF	4.35% w/w	4.51% w/w	4.56% w/w	4.57% w/w

*** Mean ±SD (n=20), ** Mean ±SD (n=5), *** Mean ±SD (n=6)**

Table No. 32: Assay and Dissolution Profile of Formulated Ubidecarenone Chewable Tablets

Time interval	Drug Content (%)	% Drug release at the end of 45 minutes *
Initial	98.14	88.65 ±0.3530
1st month	98.45	88.77 ±0.2082
2nd month	97.86	88.77 ± 0.2495
3rd month	98.54	88.45 ±0.2732

*** Mean ±SD (n=6)**


SUMMARY
AND
CONCLUSION

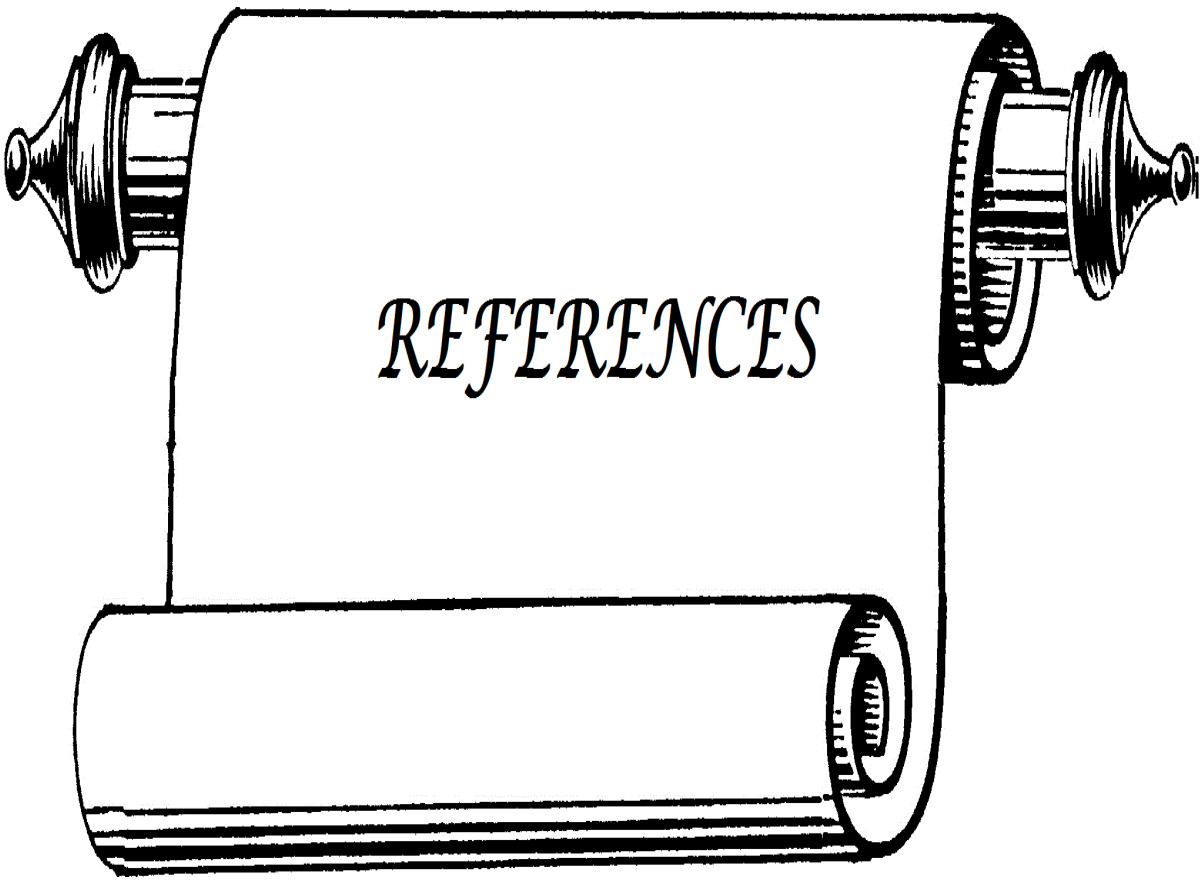
12. SUMMARY AND CONCLUSION

- The aim of the present study was to formulate Ubidecarenone chewable tablets and was achieved.
- Ubidecarenone raw material had poor flow characteristics. Hence, it was blended using directly compressible excipients which improve the flow property of the blend and chewable tablets were formulated by direct compression.
- The excipients used in the formulation were subjected to Drug- Excipient compatibility study and found that the excipients were compatible with the drug.
- Optimization study for flavouring agent was conducted and found that the Combination of Orange flavour (0.83%) and Mint flavour (0.21%) were found to be palatable.
- Optimization study for sweetening agent was conducted and as a result 1.66% of Aspartame and 0.42% of Saccharin Sodium were optimized and it was used to get good sweet taste.
- 5% of Crospovidone (Polyplasdone XL 10) was optimized to get a rapid disintegration of tablets.
- Poloxamer 407 (Lutrol Micro 127 in 0.83%) produced a drug release of 88.25% at the end of 45 minutes and it complies with USP limits. Thus it was optimized as good wetting agent.
- Colloidal Silicon Dioxide (Cabosil in 0.5%) and Sodium Stearyl Fumarate (Pruv in 0.5%) were optimized as the glidant and lubricant to produce tablets without sticking, picking and striation.
- The optimized formulation blend has a good flow property based on its angle of repose value.
- The optimized formulation blend (E III) was compressed by direct compression technique in 16 station tablet compression machine using 21 x 10 mm caplet shaped punches.
- The formulated chewable tablets were evaluated for post compression parameters and found that they were uniform in weight, thickness and hardness. The friability was within the limits.
- The disintegration time of chewable tablets for finalized batch (E III) was 1 minute 45 seconds.

- The drug content of the chewable tablets was 98.14% and is within the USP limits (90-110%).
- Drug release of 88.25% was observed at the end of 45 minutes and 99.75% at the end of 90 minutes for optimized batch (E III) and it was within the USP limits.
- The formulated chewable tablets were subjected to accelerated stability studies and the tablets were found to be stable.
- The Ubidecarenone in the form of chewable tablets (400mg) will improve the compliance of Parkinsonism patients.

❖ Future plan

- The scale up studies is required for the optimized formulation to meet the Industrial requirements.
- The bioequivalence studies in human volunteers should be conducted to know the *in vivo* performance and efficacy of the formulation.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